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**The nature of neuroticism
individual differences in psychopathology**

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The nature of neuroticism: individual differences in psychopathology

Fiona Patrick

Thesis submitted to King's College London for the degree of Doctor of
Philosophy

2018

Abstract

There is a growing support for the conceptualisation of psychopathological symptoms as continuous and dimensional with underlying transdiagnostic mechanisms. Neuroticism has been identified as a transdiagnostic candidate with particular relevance to mood and anxiety disorders. As such, this thesis explored neuroticism in two highly burdensome diseases in this bracket, major depressive disorder (MDD) and generalized anxiety disorder (GAD). Though a transdiagnostic approach can provide rich understanding, a purely dimensional system has been criticised as reductionist. Therefore, this thesis also explored self-reflection and defensive behaviour as additional lower-level factors in MDD and GAD, to examine potential disorder-specific characteristics in a multi-factor approach to disease.

This thesis firstly explores the practical applications of neuroticism as a transdiagnostic factor, piloting a research recruitment tool using self-reported neuroticism to identify individuals with GAD in chapter 3. Neural activation and individual differences in defensive behaviour was explored in chapters 4 and 5, the latter using a sample of individuals with GAD to additionally attempt a pharmacological validation of a human translation of a rodent measure of fear and anxiety. Self-reflection was explored in chapter 6 through the lens of self-criticism and self-perception, as measured by a novel adaptation of a pre-existing tool. Finally, chapter 7 takes these findings beyond MDD and GAD, contextualising neuroticism in the vulnerable dark triad (VDT) of personality.

The results of this thesis indicate support for neuroticism as a transdiagnostic factor in MDD, GAD and co-morbidity of these disorders. Neuroticism appears to play a role in maladaptive characteristic expression, as demonstrated by involvement in self-criticism levels across these disorders; further neuroticism as the ‘core’ of the maladaptive VDT was supported, though findings also indicated that other traits such as agreeableness are likely important. Interestingly, a potential adaptive role for average levels of neuroticism in healthy controls was identified, through a positive association with self-reassurance. Different characteristic expression of self-hatred and self-reassurance were shown in co-morbidity and GAD respectively, highlighting the relevance of lower-level factors in dimensional and transdiagnostic approaches to psychopathology. Identification of anterior insula activation during defensive behaviour was a key finding of this thesis and is discussed in the context of a neural network for transdiagnostic factors in MDD and GAD. The thesis also provides the first systematic review of active defensive behaviour in humans, the findings of which support animal models and prominent theories of defensive behaviour.

Acknowledgements

I would firstly like to thank my supervisors Professor Steve Williams, Professor Allan Young and Dr Adam Perkins both for the opportunity to undertake this PhD, but also for their advice, guidance and support throughout the past 3 years. I'd also like to thank the staff of the Clinical Research Facility at King's College Hospital for their help with data collection for chapter 5, especially Victor, Jasmine, Noah, Lou, Jon and the radiography team. The biggest thanks, however, is to all the individuals who gave up their time to take part in my experiments and who made this research possible.

I'd also like to thank my colleagues in the Centre for Affective Disorders and the inmates of 103 Denmark Hill past and present for sharing their academic wisdom and providing frequent distractions: Becci, Rachael, Tim, Dimos, Val, Nefize, Dil, Viktoria, Tanja, Caroline, Emma, Joseph & Sue (and the mice). Especial thanks to Lindsey and Toby, for sharing their neuroimaging expertise with me, and to Sinead for moral support (and pizza) as we both finished writing up.

I've been fortunate to have the support of an amazing group of friends throughout my PhD, who I cannot thank enough. Firstly, the Team (Cat, Liam, Andy, Alex, Laura, Claire, Tommy and Mimi) for being the best support network anyone could have. Thanks also to Jersey road (Cody, Tom, Ryan and Eddy) for making the most fun- and love-filled home, and especially to Tanya (for taking me on many holidays far away from my thesis, providing endless emotional hand-holding and being so wise) and Ash (for being wonderfully reassuring in my many panicked moments, and for reminding me it is all worth it in the end). Thank you to my family: to my mum and Mike, to Dad and Iris, and particularly to Jono, for sharing an interest in my projects and showing great patience in the face of numerous and often stupid neuroimaging questions. Finally, to Nairn for his kindness, support and patience, and for always managing to look interested when I talk about my thesis.

Abbreviations

AAL	Automated anatomic labelling
ANOVA	Analysis of variance
APT	Anxiety-related personality traits trial
AUC	Area under curve
BA	Brodmann area
BAS	Behavioural activation system
BFAS	Big five aspect scale
BIS	Behavioural inhibition system
BLA	Basolateral amygdala
BNST	Basal nucleus of the stria terminalis
BOLD	Blood oxygenation level dependent
BPD	Borderline personality disorder traits
CC	Cingulate cortex
CeA	Central amygdala
CONSORT	Consolidated standards of reporting trials
CMT	Compassionate mind training
DMN	Default mode network
DRN	Dorsal raphe nucleus
DSM	Diagnostic and statistical manual (versions 4, 5)
DT	Dark triad
FC	Frontal cortex
FFFS	Flight-fight-freeze system
FI	Flight intensity
FIQT	Fake IQ Test
fMRI	Functional magnetic resonance imaging
FSCSRs	Forms of self-criticising and self-reassuring scale
FSL	FMRIB software library
FSS	Fear survey schedule
FWE	Family-wise error
FWHM	Full width half maximum
GAD	Generalized anxiety disorder
GC	Goal-conflict
HAM-A	Hamilton anxiety rating scale
IFC	Inferior frontal cortex

IMI	Intrinsic motivation inventory
IRI	Interpersonal reactivity index
ITI	Inter-trial interval
IUS	Intolerance of uncertainty
JORT	Joystick operated runway task
LAS	Liebowitz anxiety scale
MADRS	Montgomery-Åsberg depression rating scale
MDD	Major depressive disorder
MDTB	Mouse defence test battery
MEG	Magnetoencephalography
MINI	Mini international neuropsychiatric interview (version 5.0)
MNI	Montreal neurological institute
MRI	Magnetic resonance imaging
nAChRs	Nicotinic acetylcholine receptors
NEO-FFI	NEO- five factory inventory
OFC	Orbitofrontal cortex
PAG	Periaqueductal grey
PET	Positron emission tomography
PFC	Prefrontal cortex
POMS	Profile of mood states questionnaire
PRF	Personality research form
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PSS	Perceived social stress scale
RAI	Risk assessment intensity
RCT	Randomised controlled trial
ROC	Receiver operating characteristic
ROI	Region of interest
RST	Reinforcement sensitivity theory
SA	Simple avoidance
SAD	Social anxiety disorder
SCR	Skin conductance response
SD	Standard deviation
SDM	Seed-based d mapping
SMA	Supplementary motor area
SPECT	Single positron emission tomography
SPM	Statistical parametric mapping

SPSRQ	Sensitivity to punishment and reward questionnaire
STAI	State-trait anxiety inventory
TC	Temporal cortex
TPQ	Tri-dimensional personality questionnaire
TSDI	Trait self-description inventory
VAS	Visual analogue scale
VS	Ventral striatum
VTa	Ventral tegmental area
WFU	Wake Forest University

Overview of thesis and statement of candidate's contribution to the work presented

Overview

This thesis has been prepared in line with King's College London guidelines permitting inclusion of published work in a modified thesis structure. As such, this thesis includes a general introduction and overview of aims section (chapter 1), an overview of study design and participant populations (chapter 2), a systematic review with pooled-data analysis (chapter 4), four experimental chapters (chapters 3, 5, 6 & 7) and a general discussion bringing together the findings of the whole thesis (chapter 8). The systematic review with pooled-data analysis and the four experimental chapters correspond to work that is already published, currently in peer review or in the process of being prepared for submission.

Statement of contribution

Chapter 1

The first chapter provides a general background to the work incorporated in the thesis. I wrote this chapter with feedback from Professor Allan Young and Dr Adam Perkins.

Chapter 2

Chapter 2 outlines with experimental design, ethical approval and participant demographics of the experimental work included in this thesis. I wrote this chapter and conducted the statistical analysis. I applied for the ethical approval and funding for chapters 6 and 7; the approval and funding for chapters 3 and 5 was already in place before I started my PhD. I designed the experimental procedure of chapter 6 and 7, with advice from Dr Adam Perkins. I conducted all study visits and collected all data across the four experimental chapters (with clinical advice from Professor Allan Young and fMRI advice from Professor Steve Williams in chapter 5).

Chapter 3

This chapter reports two studies: the first explores normative data for the big-5 measure of the Trait Self-Description Inventory (TSDI; Collis & Elshaw, 1998), and the second covers the piloting of an online personality measure for use in recruitment of individuals with generalized anxiety disorder (GAD) to a phase II clinical trial. The personality measure was developed by Dr Adam Perkins from the original 163-item version (Collis & Elshaw, 1998) and adapted for online use as a clinical trial pre-screening tool by Rob Davis. Dr Adam Perkins and I collected the data for study 1, and I collected the data for study 2 independently. I conducted all analysis on both sets data collected and wrote all sections of this chapter with guidance from Professors Allan Young and Steve Williams, and Dr Adam Perkins. This chapter is based on an article published in the Journal of Neuropsychiatric Disease and Treatment during my PhD, of which I am first author (Patrick, Young, Williams, & Perkins, 2018).

Chapter 4

Chapter 4 consists of a systematic review and pooled-data analysis of brain activation during human defensive behaviour. I designed the review, conducted the literature searches and data analysis and wrote all sections of this chapter with guidance from Dr Adam Perkins, Professors Allan Young and Steve Williams, Dr Lindsey Marwood and Dr Matthew Kempton. Dr Lindsey Marwood also acted as the second reviewer for study inclusion in the analysis. This chapter is an expansion of an article published in the journal of Neuroscience and Biobehavioural reviews of which I am first author (Patrick, Kempton, Marwood, Williams, Young & Perkins, 2019).

Chapter 5

This chapter presents the findings of an fMRI pharmacological trial of the effects of two anxiolytic medications on human defensive reactions in a sample of individuals with GAD and high neuroticism. I collected all data for this chapter, conducted the statistical analysis and fMRI analysis (the latter with advice and guidance from Dr Toby Wise, due to his expertise with the

analysis methodology) and wrote all sections with feedback from Professors Allan Young and Steve Williams, and Dr Adam Perkins.

Chapter 6

Chapter 6 outlines the results of an experiment investigating self-reflection (self-criticism and perception of own performance) and neuroticism in individuals with GAD and/or major depressive disorder (MDD). As stated above, I applied for the ethical approval and funding for this experiment, designed the protocol, collected all data and conducted all the statistical analysis. I adapted the Fake IQ Test (FIQT) measure for use remotely online with the help of a programmer, Rob Davis. I wrote all sections of this chapter, with guidance from my supervisors, Professors Allan Young and Steve Williams, and Dr Adam Perkins. A manuscript partially based on this chapter, of which I am joint first author, is currently in preparation for submission to the journal of Psychological Medicine.

Chapter 7

The final experimental chapter explores neuroticism as the potential ‘core’ of the vulnerable dark triad (VDT) of personality; secondary aims included investigating the relationship between self-reflection (self-criticism and performance of own perception), anxiety and the VDT. I designed the study, applied for ethical approval and financial support, and collected all data in this experiment. I also conducted all the statistical analysis and wrote all sections of this chapter, with guidance from Professor Steve Williams and Dr Adam Perkins.

Chapter 8

Chapter 8 covers the general discussion of findings from across this thesis. I wrote all sections of the discussion, with guidance from Professor Allan Young and Dr Adam Perkins.

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Chapter 1: Introduction

1.1 General introduction and rationale

1.1.1 *Personality in psychopathology*

The importance of personality in our understanding of the individual, their health and their wellbeing reaches as far back as the classical era (Barlow, Sauer-Zavala, Carl, Bullis, & Ellard, 2014). Ancient Greek approaches to medicine centred on the four humours, which were thought to influence individual differences in temperament and associated alterations in health (Arikha, 2007). Modern psychology has amassed a range of personality models, spanning from early work by Galton (Galton, 1884) and Allport (Allport & Odbert, 1936) to the foundational work of Eysenck in the 1940s (Eysenck, 1947). Freud's early distinction between temporary objective anxiety due to proximal threat and longer-term distress due to neurotic anxiety has been identified as a formative concept in the development of the field (Barlow et al., 2014; Freud, 1924). These approaches were followed by Gray's biopsychological theory of personality (Gray, 1982; McNaughton & Gray, 2000) with its distinction between fear and anxiety, and more recently the ubiquitous Five Factor Model of personality (FFM; McCrae & Costa, 1985, 1987). Building on this historical foundation, personality traits have long been explored in the context of well-being. Neuroticism is a domain-level dimension of the FFM, measuring emotional stability, and is integral part of many personality models (Barlow et al., 2014; Costa & McCrae, 1992; Eysenck, 1947). Neuroticism is a trait with prolific links to poor physical and mental health in the literature (Clark, Watson, & Mineka, 1994; Kendler, Kuhn, & Prescott, 2004; Lahey, 2009; Neeleman, Ormel, & Bijl, 2001). This thesis adopts this personality-sensitive approach to mental health, exploring the role neuroticism may play in psychopathology and further investigating how additional individual differences can improve our understanding of transdiagnostic mechanisms in mood and anxiety disorders.

1.1.2 Mood and anxiety disorders

The prevalence rates of mood and anxiety disorders are some of the highest in psychiatry, with estimates of lifetime prevalence of around 20.8% and 28.8% respectively (Kessler et al., 2005). This thesis has a focus on two disorders within this bracket, major depressive disorder (MDD) and generalized anxiety disorder (GAD). Though mood disorders typically include dysthymia and bipolar disorder, and anxiety incorporates a wide range of pathologies such as social phobia, specific phobia and panic disorder, these diagnoses are beyond the scope of the experimental work in this thesis. MDD presents episodically, and is typified by low mood, impaired functionality and anhedonia (Otte et al., 2016). As well as being highly prevalent, MDD diagnosis holds one of the highest burdens in psychiatry (Ferrari et al., 2013), with profound impact on quality of life (Wells et al., 2002). GAD is defined by extreme tension, worrying and somatic anxiety symptoms not limited to specific situations (Baldwin et al., 2005); as with MDD, this disorder is both prevalent in the population, and greatly disabling (Wittchen, 2002). MDD and GAD are also highly co-morbid disorders (Moffitt et al., 2010, 2007; Takahashi, Roberts, Yamagata, & Kijima, 2015; Wittchen, 2002). Co-morbidity between these diagnoses is not only common but is also associated with greater impairment than presence of either disorder alone (Grant et al., 2005; Kessler, DuPont, Berglund, & Wittchen, 1999). These disorders are also both closely associated with raised levels of neuroticism (Michael Bagby & Rector, 1998; Kotov, Gamez, Schmidt, & Watson, 2010; Lahey, Zald, Hakes, Krueger, & Rathouz, 2014; Mitchell et al., 2007), with evidence of a shared genetic base (Hettema, Prescott, & Kendler, 2004; Mackintosh, Gatz, Wetherell, & Pedersen, 2006). As outlined here, MDD and GAD are highly burdensome disorders which share a complex relationship. As such, a better understanding of the shared and distinct mechanisms between these disorders would be of benefit, with potential impact on identification and treatment of these disabling disorders.

1.1.3 Transdiagnostic mechanisms in psychopathology

Categorical classification of disorders has long been the norm in the medical model of disease and psychiatry has traditionally followed this approach, regarding disorders as distinct entities

(Caspi & Moffitt, 2018). The asylum system of early-modern psychiatry made patient behavioural management of greater import than nosology, meaning it wasn't until after WWII that a unified approach to diagnosis was undertaken (Blashfield, Keeley, Flanagan, & Miles, 2014). The highly categorical stance this approach took is clear in the structure of the Diagnostic and Statistical Manual of Mental Disorders (DSM) series (American Psychiatric Association, 1952, 1968, 1980, 1987, 1994, 2000), with the improved reliability of DSM-III leading to a growth in treatments increasingly focused on individual disorders (Norton, 2012). The most recent version however, the DSM-5 (American Psychiatric Association, 2013), has provided scope for movement away from strictly categorical and independent disorders (Kreuger & Eaton, 2015) to a more dimensional approach. Though not a new idea (e.g. Barlow, 1988; Kendell, 1969, 1975; Maser & Cloninger, 1990; Widiger, 1992) this move is in line with a growing body of evidence supporting a different approach to understanding mental health, conceptualising symptoms as continuous and dimensional with underlying transdiagnostic mechanisms (Brown & Barlow, 2005; Brown & Barlow, 2009; Carragher, Krueger, Eaton, & Slade, 2015; Caspi & Moffitt, 2018). At a broader level, this reflects a debate in psychiatry as to whether disorders should be understood and depicted by their causes, or descriptively by their symptom profiles (Zachar & Kendler, 2007).

Proponents of the transdiagnostic approach propose broad-domain dimensional constructs with applicability across a range of disorders as a better way of understanding and collating disorders dependent on their underlying mechanisms (Sauer-Zavala et al., 2017). Advocates also argue that transdiagnostic dimensional approaches minimise loss of complex and pertinent information that can be caused by categorical approaches, as a disorder is only either entirely present or absent (Carragher et al., 2015). Importantly, dimensional and categorical approaches are not necessarily mutually exclusive. Though a transdiagnostic dimensional approach can provide a rich understanding of symptom presentation and severity, as well as avoiding the tendency to obscure clinically relevant co-morbidities (Brown & Barlow, 2005), in practice the ability to provide some distinction between disorders is important, both in clinical work and research (Brown & Barlow, 2005; Goldberg, 2000). Therefore, theoretically both concepts may be used in tandem as is

somewhat reflected in the DSM-5 approach to diagnosis (American Psychiatric Association, 2013). Though still largely reliant on presence/absence descriptors, the DSM-5 includes severity specifications, and further allows for identification of cross-diagnosis symptoms such as the ‘with anxious distress’ specifier, which is can be applied across depressive and bipolar related disorders (American Psychiatric Association, 2013; Regier, Kuhl, & Kupfer, 2013). Inclusion of overarching transdiagnostic factors in diagnostic tools such as the DSM may improve utility in the identification of vulnerability and prevention of disorders. This would allow their purpose to move beyond disease description alone, as some suggest is the extent of their current role (Brown & Barlow, 2005).

1.1.3.1 Transdiagnostic mechanisms in mood and anxiety disorders

The move towards transdiagnostic mechanisms underlying mood and anxiety disorders was given fresh impetus by the instigation of the Research Domain Criteria framework (Insel et al., 2010; Sanislow et al., 2010; Watkins, 2015), which has a strong dimensional focus. As aforementioned, mood and anxiety disorders have significant levels of co-morbidity (Barlow et al., 2014; Brown, Campbell, Lehman, Grisham, & Mancill, 2001); there has been speculation that GAD in particular has greater overlap with mood disorders than other anxiety disorders (Brown, Chorpita, & Barlow, 1998). Some argue that high levels of co-morbidity indicate low discriminant validity between diagnoses (Andrews, 1990; Brown & Barlow, 2009); if so, then considering transdiagnostic mechanisms between these diagnostic categories is key in understanding disorder presentation. Biological overlap between disorders also supports a transdiagnostic approach to psychiatry. For example, a recent meta-analysis indicated commonalities in neural mechanisms across mental health pathology, though little specificity in relation to diagnoses was shown (Sprooten et al., 2017). Further, exploration of the genetic correlations between depression and anxiety disorders have indicated a close relationship between these diagnoses (Middeldorp, Cath, Van Dyck, & Boomsma, 2005; Zachar & Kendler, 2007).

The successful application of behavioural treatments across multiple conditions is also cited as evidence for underlying transdiagnostic mechanisms. For example, suppression and acceptance

techniques (Campbell-Sills, Barlow, Brown, & Hofmann, 2006) and the successful use of Cognitive Behavioural Therapy (Norton, 2012) across different categories of anxiety and depressive diagnoses supports an underlying mechanistic similarity. Pharmacological interventions have also successfully been applied to multiple conditions. Though indicated for depression, antidepressants are often successfully used in the treatment of some anxiety disorders (Bakker, Van Balkom, & Spinhoven, 2002; Offidani, Tomba, & Fava, 2013). This is supported by several systematic reviews of anxiety treatment (Bandelow et al., 2015; Ravindran & Stein, 2010; Zohar & Westenberg, 2000) and the prominence of antidepressants such as selective serotonin re-uptake inhibitors in the clinical guidelines for treatment of both GAD (Baldwin et al., 2005) and MDD (Kennedy, Lam, Cohen, & Ravindran, 2001). A transdiagnostic approach has also been lauded for its potential to improve the flexibility of diagnostic tools (Watkins, 2015), and to impact cost-effectiveness (Caspi & Moffitt, 2018).

A better understanding of the transdiagnostic approach is key not only for clinical intervention, but for research methodology (Barlow et al., 2014). Research commonly uses categorical diagnostics when making decisions about eligibility and ineligibility for trial enrolment, often only including individuals meeting strict diagnostic criteria for (usually) one disorder. This is not reflective of the huge degree of co-morbidity observed in psychiatry (Barlow et al., 2014; Brown et al., 2001; Caspi & Moffitt, 2018), particularly in those seeking treatment (Wise et al., 2016). Nor does this sampling method address the evidence suggesting treatment efficacy across diagnostic categories (Campbell-Sills, Cohan, & Stein, 2006; Offidani et al., 2013; Watkins, 2015). As such, recruitment to research trials could be more focused on transdiagnostic factors, and in turn general vulnerabilities to psychopathology (Barlow et al., 2014) to capture and reflect the psychiatric population more accurately. Transdiagnostic approaches to research have not been popular, possibly due to concerns about attaining adequate power for analysis in Randomised Controlled Trials, which remain the gold-standard for research. A change in recruitment towards identification of transdiagnostic mechanisms instead of purely categorical diagnosis is risky

without an evidence base for the underlying mechanisms. The basic research in to transdiagnostic mechanisms is crucial before fundamental change to research practice can be considered.

Conceptually, a transdiagnostic approach suggests that abnormal functioning of transdiagnostic mechanisms can result in symptomology across several diagnoses, as the same mechanisms underly a spectrum of disorders and several different mechanisms can play a role in symptom expression in each disorder (Lahey et al., 2014). In this model, disorders reflect varied manifestations of deficits in these overarching transdiagnostic mechanisms, dependent on experience of specific environmental, biological or genetic etiological factors (Brown & Barlow, 2009). Research has started to explore a range of transdiagnostic mechanisms in psychopathology through the identification of overarching high-order traits (i.e. factors associated with broad biological and environmental constructs of personality; Brown & Barlow, 2009) with commonality across disorders (Ellard, Fairholme, Boisseau, Farchione, & Barlow, 2010). This work has proposed different putative candidates, such as positive/negative valence, internalizing vs. externalizing temperaments, differences in arousal/regulatory systems and abnormal defensive behaviours (Insel et al., 2010; Watkins, 2015) and some have even suggested a general factor of psychopathology, analogous to the general factor of intelligence (Lahey et al., 2012).

1.1.3.2 Neuroticism as a transdiagnostic factor in mood and anxiety disorders

Neuroticism is a high-order trait within the hierarchical organisation of personality (Costa & McCrae, 1992), and features in almost all of three- and five- factor models of personality (Costa & McCrae, 1992; Eysenck, 1947; Hettema et al., 2004; Lahey, 2009). Neuroticism incorporates individual differences in emotional response to factors such as threat, loss or frustration (Lahey, 2009). Individuals with high levels of neuroticism are conceptualised as holding anxious, unstable, worrying, vulnerable and self-defeating attitudes (Costa & McCrae, 1992; McCrae & John, 1992). Though there is some debate, neuroticism is generally considered stable through adulthood (Ormel, Rosmalen, & Farmer, 2004; Viken, Rose, Kaprio, & Koskenvuo, 1994), making it a particularly interesting transdiagnostic candidate.

Neuroticism has been identified as a key vulnerability factor for mental ill-health (Bienvenu & Stein, 2003; Kotov et al., 2010; Navrady, Adams, Chan, Ritchie, & McIntosh, 2018; Sutin, Beason-Held, Dotson, Resnick, & Costa Jr, 2010), with close links to many psychiatric conditions (Clark et al., 1994; Lahey, 2009; Neeleman et al., 2001; Opel et al., 2018). Particularly large effect sizes are noted in mood and anxiety disorders (Kendler et al., 2004; Khan, Jacobson, Gardner, Prescott, & Kendler, 2005; Malouff, Thorsteinsson, & Schutte, 2005). Specifically, robust links between neuroticism and both MDD (Bagby & Rector, 1998) and GAD (Kotov et al., 2010; Lahey, 2009) have been observed. Indeed, elevated scores of as little as one standard deviation have been associated with estimates of up to 90-100% increase in risk of developing MDD in the 12 months following assessment (Kendler, Kessler, Neale, Heath, & Eaves, 1993). In addition, neuroticism is also associated with increased co-morbidity of mental health syndromes (Lahey, 2009; Moffitt et al., 2007; Takahashi et al., 2015), explaining up to 45% of observed co-morbidity between anxiety diagnoses and MDD (Khan et al., 2005). As well as increasing risk of disorder development and the complexity of disease presentation, heightened levels of neuroticism have also been associated with poorer prognosis following diagnosis (Clark et al., 1994).

Neuroticism has been linked to behaviours and processes related to the development, maintenance and symptom profile of anxiety and depressive disorders. High levels of neuroticism have been associated with differences in cognitive-emotional functioning (Cremers et al., 2010), negative attention biases (Derryberry & Reed, 1994), memory biases (Martin, 1985), rumination (Roberts, Gilboa, & Gotlib, 1998) and use of maladaptive coping strategies (Fickova, 2001). Neuroticism also largely shares a neural network with mood and anxiety disorders; raised neuroticism has been related to altered amygdala, anterior cingulate cortex and prefrontal activity (Cremers et al., 2010), whilst aberrant connectivity between the cingulate and prefrontal regions (Keightley et al., 2003) and in within the limbic-frontal circuitry (Sutin et al., 2010) are linked to individual differences in neuroticism. Abnormal activity and connectivity several of these areas has also been linked to GAD (Hilbert, Lueken, & Beesdo-Baum, 2014) and depressive disorders (Nestler et al., 2002). More recently, a relationship between polygenic load for neuroticism and altered

cortical surface area has been indicated, highlighting changes in anterior cingulate cortical surface area (Opel et al., 2018); this is a region closely linked to GAD, for example evidence suggests that pre-treatment activation in this region can predict response to pharmacological treatment (Nitschke et al., 2009). The precuneus and inferior parietal cortex were also identified in the study, which the authors highlight as parts of the Default Mode Network (DMN) (Opel et al., 2018). DMN circuitry has been associated with negatively valenced self-generated thought, a process also linked to neuroticism due to the characteristic worry and rumination of this personality trait (Perkins, Arnone, Smallwood, & Mobbs, 2015). Importantly, these cortical surface changes were associated with neuroticism in both healthy controls and those diagnosed with MDD (Opel et al., 2018), suggesting presence of neuroticism alone does not necessarily determine presence of MDD.

Following, there is considerable conceptual and theoretical support for neuroticism as an underlying transdiagnostic mechanism in mood and anxiety disorders. Indeed, some researchers in the field have directly proposed neuroticism as a key transdiagnostic mechanism (e.g. Brown & Barlow, 2009), whilst others have suggested closely related processes, such as repetitive negative thought (Watkins, 2015) which aligns with the worry and rumination characteristic in high levels of neuroticism (Costa & McCrae, 1992).

1.1.4 A multi-level approach to transdiagnostic mechanisms

However, by definition transdiagnostic factors do not provide much specificity beyond a general risk for broad categories of psychopathology. Neuroticism does indeed have poor specificity in psychiatry (Claridge & Davis, 2001; Kotov et al., 2010; Ormel et al., 2004), as indicated by its relationship with a substantial and varied number of conditions (Lahey, 2009). Overemphasis or sole reliance on neuroticism (or any single high-order domain) in psychopathology has been critiqued as reductionist (Brown & Barlow, 2009), potentially ignoring important information regarding risk. For example, the likelihood of developing specific negative complications such as suicidality within disorders is not necessarily fully explained by a broad high-order factor such as neuroticism (Brown & Barlow, 2009).

Neuroticism is therefore perhaps best posed as a moderator, impacting and influencing expression of characteristics specific to diagnostic categories and disorders (Claridge & Davis, 2001). A multi-level approach to transdiagnostic factors may provide something of a solution to the inexact nature of high-order transdiagnostic candidates such as neuroticism. This approach would combine a broad-level assessment of the overarching high-order factor with investigation of lower-level (i.e. specific psychological facets, that do not generalize across disorders) factors in a two-tiered approach. This could identify enduring transdiagnostic candidates associated with general risk of pathology, as well as allowing current assessment of temporally present symptoms (Caspi & Moffitt, 2018). Several lower-level factors have been suggested for this role, including measures of current fear of uncertainty or current distress (Barlow et al., 2014). This would have neuroticism as a “potent general indicator of psychopathology” (Claridge & Davis, 2001, p385), but would include lower-order variation within neuroticism for provision of additional key information and meaningful differentiations in mood and anxiety disorders. This suggests that exploration and inclusion of individual variation in alternate but related domains alongside overarching high-order domains such as neuroticism may determine specific psychopathological experiences (Cox, Enns, Walker, Kjernisted, & Pidlubny, 2001; Paunonen, 1998).

Though the relationship between neuroticism and both MDD and GAD is well supported, the nature of individual differences within this putative relationship are less well established. Assessing potential lower-tier factors in a multi-dimensional approach to these disorders would provide the groundwork for future targeting of fundamental mechanisms (Watkins, 2015) and would have applicability to tailored treatment regimes, especially in those with co-morbidity. Transdiagnostic factors would also be of use in research recruitment, as non-invasive screening of self-reported neuroticism could highlight groups of individuals eligible for clinical trials in a non-invasive manner. Two prominent lower-order candidates are explored alongside neuroticism in this thesis: defensive behaviours and negative self-reflection.

1.1.4.1 Defensive behaviour

Defensive behaviour arises from exposure to threatening or conflicting stimuli. One of the prominent theories of defensive behaviour in humans is Reinforcement Sensitivity Theory (RST; Gray, 1982; McNaughton & Corr, 2004; McNaughton & Gray, 2000). Developed in response to rejection of the single-drive hypothesis of reinforcement behaviour (e.g. Hull, 1952), the original RST featured two systems: The Behavioural Approach System (BAS, primarily concerned with appetitive stimuli) and the Behavioural Inhibition System (BIS, controlling defensive approach of conflicting and negative stimuli) (McNaughton & Gray, 2000). This original model has since been revised, and it is this revised version that is adopted in this thesis. Several changes were made in the revision, but a key change is the inclusion of the Fight-Flight-Freeze System (FFFS) and the separation of the responsibilities of the BIS such that the FFFS takes responsibility for avoidance of aversive stimuli, whilst the BIS retains a focus on conflict situations requiring defensive approach (Jackson, 2009; McNaughton & Corr, 2004). The BAS, BIS and FFFS are orthogonal but functionally interactive systems (Corr, 2002; Jackson, 2009; McNaughton & Corr, 2004), underlying behaviour, mood and appetitive functioning (Hundt, Nelson-Gray, Kimbrel, Mitchell, & Kwapil, 2007). This thesis focuses on the BIS and FFFS arms of the RST model; though the BAS is arguably relevant to several psychiatric conditions (Bijttebier, Beck, Claes, & Vandereycken, 2009), it is beyond the scope of this thesis.

With the separation of the BIS and FFFS arms came a conceptual distinction between anxiety and fear (Jackson, 2009; McNaughton & Corr, 2004). As the BIS has a focus on conflicting situations that may require approach, anxiety is thought to be a function of this system; as the FFFS response specifically to aversive or threatening stimuli, fear reactions are considered part of this arm (Jackson, 2009; Perkins, Kemp, & Corr, 2007). This conceptual separation is also thought to continue at the neural level, with interactive but partially separable neural streams for BIS (anxiety) and FFFS (fear) response proposed (McNaughton & Corr, 2004). Theorists propose a defensive avoidance (i.e. responding to aversive stimuli, using the FFFS) network with direct relation to the proximity of threat. When threat is very distant, neural activation is largely

prefrontal (specifically, ventral PFC areas) but moves towards the midbrain as threat approaches (through the anterior cingulate, amygdala and medial hypothalamus) before reaching the PAG when threat is highly proximal (McNaughton & Corr, 2004). Defensive approach (i.e. conflicting situations requiring further information gathering, using the BIS) similarly progresses from forebrain to midbrain regions as threat is approached (though the forebrain regions are dorsal rather than ventral) which is followed by the posterior cingulate cortex and a crucial distinction in the involvement of the septo-hippocampal system, before the two systems somewhat converge at close proximity of threat, with amygdala, medial hypothalamus and PAG activation (McNaughton & Corr, 2004). Figure 4 in chapter 4 gives a visual representation of this model.

Defensive behaviour has strong relevance to psychiatry, as hypo- and hyper-activation of defensive behaviour systems has been linked to psychopathology (Bijttebier et al., 2009; Hundt et al., 2007). Abnormally overactive BIS function is thought to have a relationship with GAD and MDD (Hundt et al., 2007; Kasch, Rottenberg, Arnow, & Gotlib, 2002), whilst FFFS hyperactivity is believed to be associated with fear-based disorders such as panic disorder (Bijttebier et al., 2009; Jackson, 2009; McNaughton & Corr, 2004). The RST model has relevance to treatment, as the avoidance behaviours typical of the FFFS can prevent exposure learning about the perceived threat (LeDoux, Moscarello, Sears, & Campese, 2017) as theoretically could abnormal approach functioning in a hyperactive BIS system. There is a strong case for active engagement in therapy for anxiety disorders (Glenn et al., 2013) and evidence that suppression of areas involved with the BIS and FFFS can improve growth of coping skills and assist exposure (LeDoux et al., 2017).

Substantial individual differences in defensive behaviour have been noted (Corr, 2013). Gray's original theory posited characteristic overreaction to negative stimuli as the base of BIS (Gray, 1982), which has more recently been interpreted as analogous to neuroticism (Barlow et al., 2014). Neuroticism is posited as underlying differences in the perception of defensive distance (i.e. distance from threat; McNaughton & Gray, 2000), thus resulting in over- or under- active response of the BIS and FFFS, though these findings are not unanimous in the literature (e.g. Perkins et al., 2007). Maladaptive avoidance is characteristic of several disorders and maladaptive

behaviours beyond anxiety and fear- based pathologies, including OCD, suicidal tendencies and autism (Delgado, Olsson, & Phelps, 2006; LeDoux et al., 2017; Servatius, 2016) supporting this factor as a potential lower-order transdiagnostic candidate with differential indications between disorders (e.g. Bijttebier et al., 2009).

Much of the current literature exploring defensive systems and their neural architecture has relied on animal models (Kirlic, Young, & Aupperle, 2017). Though this animal work has often supported the involvement of regions posited by RST in humans, such as the amygdala, PAG and hippocampus (Choi & Kim, 2010; Fanselow, 1994; Kirlic et al., 2017; Möller, Wiklund, Sommer, Thorsell, & Heilig, 1997), replication in humans has not always been successful or straightforward (e.g. Blanchard, 2017; Corr, 2002). As such, improved paradigms measuring defensive systems in humans and replication of animal work would be an important step for the field.

1.1.4.2 Negative self-reflective processes and attitudes

Negative self-reflection is often highlighted as a core component of MDD and anxiety disorder pathology (Ingram, Kendall, Smith, Donnell, & Ronan, 1987; Woodruff-Borden, Brothers, & Lister, 2001) as well as psychopathology more broadly, as demonstrated in eating disorders (Dunkley & Grilo, 2007). Self-criticism is a form of negative self-reflection characterised by intense feelings of worthlessness, guilt and inability to achieve desired standards (Hermanto et al., 2016) and is associated with greater social dissatisfaction (Kopala-Sibley, Zuroff, Hankin, & Abela, 2015). Self-criticism is thought to sit within the broader domain of neuroticism (Cox, MacPherson, Enns, & McWilliams, 2004; Coyne & Whiffen, 1995). This is reflected in the close association between neuroticism and self-critical behaviour, feelings of inadequacy and higher sensitivity to the criticism of others (Lahey, 2009), and in evidence suggesting that self-criticism is predicted by neuroticism level (Mongrain, 1993).

High levels of self-criticism are associated with MDD and anxiety disorders (Ehret, Joormann, & Berking, 2015; Hermanto et al., 2016), including Social Anxiety Disorder (SAD) and, to a lesser

degree, panic disorder (Iancu, Bodner, & Ben-Zion, 2015). There is also a high degree of overlap in brain regions linked to MDD, anxiety disorders and emotional regulation more broadly, with those involved in self-critical thought processes (St. Germain & Hooley, 2012). Further, self-criticism may also increase the risk of co-morbidity and contribute to negative psychosocial outcomes (Kopala-Sibley et al., 2015). Self-criticism may also be predictive of poorer treatment outcomes and increased susceptibility of relapse (Blatt, 1995; Hermanto et al., 2016). Additionally, the level of reduction in self-criticism achieved during therapeutic treatment has been shown to be a good predictor of treatment success in pathologies such as MDD (Blatt, 1995; Ehret et al., 2015; Rector, Bagby, Segal, Joffe, & Levitt, 2000). Self-criticism is thought to have a particular impact on therapeutic models with a strong interpersonal focus (Marshall, Zuroff, McBride, & Bagby, 2008).

There is some dispute as to the relative roles of neuroticism and self-criticism in psychopathology. Some have proposed self-criticism holds a direct association with psychopathology which is maintained when neuroticism is controlled for (Iancu et al., 2015), as is proposed in PTSD (Cox et al., 2004), whilst others have proposed self-criticism is an aspect of neuroticism (Coyne & Whiffen, 1995) with mental health pathology arising from overarching neuroticism (Lahey, 2009). The role of self-criticism in specific pathology expression is also contested; specifically, whether self-criticism has an interaction with MDD that is not shared with anxiety disorders such as social phobia (Blatt, 2004). Alternate evidence suggests that though self-criticism may be higher in different conditions, the evidence suggesting that it can predict diagnostic category is poor (Cox et al., 2000). As both MDD and GAD have a strong relationship with neuroticism (Lahey, 2009), exploration of variations in self-criticism may reveal more about the relationship between neuroticism and psychopathology (Coyne & Whiffen, 1995), as well as pathological expression. A clear understanding of the role of neuroticism in self-criticism and how this varies across disorders would be informative and could bolster our knowledge of self-criticism as a lower-order factor with applicability to a two-tier assessment of transdiagnostic factors in MDD and GAD. Given non-specificity of neuroticism, and the relationship between self-criticism and

treatment outcomes (Blatt, 1995; Hermanto et al., 2016) more awareness of self-criticism in pathology is of considerable clinical interest.

Perception of own performance and judgement of own ability are forms of negative self-reflection with an association with self-critical attitude. Individual differences in perception of performance may reflect biases in self-referent cognition, which underlie personality traits such as ‘pessimism’ (Greenwald, 1980; Nuttin & Greenwald, 1968). When analysed with relation to dimensions of personality, pessimism is associated with neuroticism (Marshall, Wortman, Kusulas, Hervig, & Vickers Jr, 1992); this suggests that individual differences in perception of performance may be meaningfully related to level of neuroticism. Indeed, previous research has linked (over) confidence in own ability to stable personality traits such as extraversion (Schaefer, Williams, Goodie, & Campbell, 2004). There is some evidence to link low levels of neuroticism with higher self-confidence (Cheng & Furnham, 2002), though this is disputed (Pulford & Sohal, 2006), indicating the importance of exploring this area further.

There is evidence to suggest that perceptions of performance are altered in anxiety and mood disorders. Depressed individuals have been shown to overestimate poor performance (Wener & Rehm, 1975) and have preferential recollection of punishment over reward when given feedback on performance (Nelson & Craighead, 1977). This may reflect a tendency towards negative appraisal in self-referential tasks (Beck, 1967) due to the negative schema typical of depression (Fu, Koutstaal, Fu, Poon, & Cleare, 2005) or possibly due to maladaptive counterfactual thinking processes, resulting in altered perception of self relative to others (Broomhall, Phillips, Hine, & Loi, 2017; Buunk & Gibbons, 2006). This aberrant self-referencing is so closely tied to depression in the literature that it has been described as part of the “mental landscape of depressed individuals” (Broomhall et al., 2017, p57). The relationship between negative judgements of own performance and anxiety disorders are less well researched. There is evidence to suggest that social phobia is associated with viewing the self negatively from an observer’s perspective (Werner et al., 2012). It is sometimes argued that self-criticism as associated behaviour is limited to certain settings in anxiety (Cox et al., 2000; Werner et al., 2012), however this research has

focused on social anxiety which by nature is highly situational. The relationship between poor perception of own ability and self-critical attitude has not had much focus in the literature, though understanding how the two are linked across different disorders would be informative when considering multi-level transdiagnostic fundamental mechanisms.

Clearly, self-reflective processes such as self-criticism and perceptions of own performance are pertinent in mood and anxiety disorders, though the precise nature of this relationship and the role of neuroticism within it is uncertain. In particular, how self-reflective processes differ depending on neuroticism level across affective disorders is of interest. Currently most self-reflection tools involve self-report questionnaires with global reflection of past experience. Self-report measure may be insensitive to change (Offer, Kaiz, Howard, & Bennett, 2000; Orfei, Robinson, Bria, Caltagirone, & Spalletta, 2008). This may be a particular issue in neuroimaging studies, which often require the individual to engage in imaginative states (for examples, see Longe et al., 2010; Wagner, Schachtzabel, Peikert, & Bär, 2015) and rely on the assumption that these are equivalent to real states. Though there is some evidence of an overlap, the validity of this approach is questionable (Klein & Gangi, 2010; Prigatano & Fordyce, 1986). As such, development of a tool with less reliance of global self-report would be advantageous for the field.

1.1.5 Neuroticism and maladaptive personality: the vulnerable dark triad

The first part of this thesis has a focus on MDD and GAD, and the role of self-criticism and neuroticism within and across these pathologies. The second section moves beyond anxiety and mood disorders by considering the role of neuroticism as a transdiagnostic mechanism in maladaptive personality.

The vulnerable dark triad (VDT) is a set of interrelated and co-occurring personality constructs (Miller, Dir, et al., 2010). Forming a contrast to the original dark triad (DT), the VDT is primarily associated with emotional instability, affective dysregulation and interpersonal antagonism (Miller, Dir, et al., 2010; Paulhus & Williams, 2002), and consists of the construct-triad of vulnerable narcissism, secondary psychopathy and borderline personality disorder traits (BPD)

(Miller, Dir, et al., 2010). Various aspects of VDT constructs are associated with risk for negative outcomes. For example, experience of anxiety and depression have been linked to secondary psychopathy (Miller, Dir, et al., 2010; Neria, Vizcaino, & Jones, 2016), whilst clinically diagnosed BPD has been shown to predict lifetime substance abuse in women (Feske, Tarter, Kirisci, & Pilkonis, 2006), and vulnerable narcissism is associated with greater perceived stress and poorer mental resilience (Annen, Nakkas, Bahmani, Gerber, & Brand, 2017). A link between narcissism (though not explicitly vulnerable narcissism) and suicide has also been noted (Miller, Widiger, & Campbell, 2010). The VDT has also been linked directly to maladaptive social behaviour, such as religious fundamentalism (Unterrainer et al., 2016), whilst the affective instability and dysregulation typical of the VDT constructs has been linked to perpetrated and sustained interpersonal partner violence (Dugal et al., 2018). Given the characteristic emotional instability associated with the VDT (Miller, Dir, et al., 2010), the relationship between VDT constructs and experience of depression and anxiety (Miller, Dir, et al., 2010; Neria et al., 2016; Paulhus & Williams, 2002) and the well-documented role of neuroticism as a risk factor in mood and anxiety disorders (Lahey, 2009; Martin, 1985), it is perhaps unsurprising that neuroticism has been posited as the ‘core’ of this personality triad (Jones & Figueredo, 2013; Miller et al., 2017).

The FFM features in much of the research surrounding dark personalities, and has on occasion even been used as a method of supporting and validating research tools in this area (for an example, see Lynam, Whiteside, & Jones, 1999). The clear majority of research to date has focused on the DT, with far less work centring on the VDT. Around 30-65% of variance in the DT is thought to arise from the FFM traits (O’Boyle, Forsyth, Banks, Story, & White, 2015). Low agreeableness is considered a cornerstone of the DT (Furnham, Richards, & Paulhus, 2013; Jakobwitz & Egan, 2006; Lee & Ashton, 2005), though high levels of extraversion and low conscientiousness are also cited (Grigoras & Wille, 2017). Though the available literature covering the VDT as a whole is modest, presence of a relationship between neuroticism and the individual constructs of the VDT has been shown. Secondary psychopathy and vulnerable narcissism are both robustly associated with high neuroticism (Jakobwitz & Egan, 2006; Miller,

Dir, et al., 2010). BPD however has a more varied relationship to neuroticism, with some evidence indicating high neuroticism is associated with BPD traits (Clarkin, Hull, Cantor, & Sanderson, 1993; Morey & Zanarini, 2000), whereas others posit low neuroticism as more typical (Miller, Dir, et al., 2010). Neuroticism is also thought to form one of the key factors differentiating between DT and VDT profiles. Low levels of neuroticism are considered prominent in primary psychopathy (DT) whereas high levels of neuroticism are associated with secondary psychopathy (VDT) (O'Boyle et al., 2015).

The associations between the VDT constructs and neuroticism are indicative of the malignancy of the VDT profile. As aforementioned, to date there has been a paucity of research on the VDT relative to its counterpart, the DT. The negative associations of neuroticism in regard to development, maintenance and co-morbidity of psychopathology (Bienvenu & Stein, 2003; Clark et al., 1994; Kendler et al., 2004; Khan et al., 2005; Kotov et al., 2010; Lahey, 2009; Moffitt et al., 2007; Navrady et al., 2017; Sutin et al., 2010) make exploration of this higher-order dimension imperative in the context of malignant personality profiles such as the VDT. This is especially pertinent given the negative psychosocial outcomes of VDT constructs (Dugal et al., 2018; Feske et al., 2006; Miller, Dir, et al., 2010; Miller, Widiger, et al., 2010; Neria et al., 2016; Unterrainer et al., 2016), and the insufficient research covering this pernicious triad. How neuroticism relates to expression of different components of the VDT would also provide an interesting addition to our understanding of neuroticism as the root of mood and anxiety disorder pathology.

1.1.6 Aims and objectives

The overall aim of this thesis is to clarify the transdiagnostic role of neuroticism in MDD, GAD and maladaptive personality, and to identify variation in the lower-order constructs of self-reflection and defensive behaviours between disorders, to provide more in-depth information about psychological functioning in a multi-factor approach. This would be highly informative in the context of targeting fundamental active mechanisms, providing potential for more flexible treatment approaches with applicability across conditions. A move towards treatments that remedy multiple diagnoses is desirable, as this method is more cost-effective and promotes

individualized care (Ellard et al., 2010). A multi-factor transdiagnostic approach may also outline targets for intervention in a more efficacious manner than the current approach. This overarching aim is addressed in a series of smaller steps:

1.1.6.1 Chapter 2

Overview of thesis methodology.

1.1.6.2 Chapter 3

Firstly, the practical application of a transdiagnostic mechanistic approach to research is explored. Achieving recruitment targets in clinical-type trials is one of the biggest hurdles in research (Borschmann, Patterson, Poovendran, Wilson, & Weaver, 2014; Kasenda et al., 2014; McDonald et al., 2006). Recruitment through clinical services is difficult and can be inefficient (Sullivan, 2004; Wise et al., 2016). Recent governmental frameworks have highlighted the importance of widening participation and adopting digital technology to generate study populations (Department of Health and Social Care, 2017). Chapter 3 investigates whether it is possible to efficiently identify candidate participants for a clinical trial with strict eligibility criteria, using an online self-report measure of neuroticism. Self-report measures of neuroticism are non-invasive, quick to complete and can be conducted with little input from research staff; evidence that these tools can successfully and accurately identify a group of individuals would both be a boon to research and would additionally provide some insight in to the real-world application of transdiagnostic mechanisms in research. Chapter 3 is based on a publication produced during my PhD, which can be found in the appendices.

1.1.6.3 Chapters 4 & 5

Having explored neuroticism as a practical transdiagnostic mechanism, chapters 4 and 5 initiate investigation of defensive behaviour as a lower-order mechanism in anxiety. Chapter 4 forms the initial stage of this objective. Despite a set of clear predictions regarding neural involvement, much of the research in defensive behaviour has focused on animal models (Kirlic et al., 2017). As such, a synthesis of the available human neuroimaging data on defensive behaviours would

be useful to provide an overview of not only the neural involvement identified, but also the available paradigms for assessing active defensive behaviours. This was to not only demonstrate the key neural areas involved for use in the following chapter, but also to assess the strengths and weaknesses of human defensive behaviour tools.

Chapter 5 aims to apply this knowledge and the predictions of RST (McNaughton & Corr, 2004) to a neuroimaging pharmacological anxiolytic study of individuals with high neuroticism who meet the criteria for GAD. The purpose was foremostly to identify whether the same brain regions were activated as those identified in chapter 4. As identified in chapter 4, there is a paucity of defensive behaviour trials using individuals with anxiety making this a novel contribution to the field. Secondly, this chapter aimed to explore role of anxiolytics in defensive behaviour in individuals with high levels of neuroticism. Finally, this chapter used the Joystick Operated Runway Task (JORT; Perkins et al., 2013) to measure defensive behaviour. The JORT has not been investigated for use in pharmacotherapeutic neuroimaging trials, nor has it been validated in anxious individuals. Therefore, the final aim of chapter 5 was to provide insight in to the JORT as a useful tool through the application of anxiolytics in comparison to placebo, following the notion that anxiolytic medication should reduce defensive behaviour as indicated in a previous (non-fMRI) trial (Perkins et al., 2013).

1.1.6.4 Chapter 6

Chapter 6 investigates negative self-reflection another potentially informative lower-order trait in GAD, MDD and co-morbidity. Self-criticism is a considered a vulnerability involved in the development and maintenance of psychopathology (Hermanto et al., 2016), with links to neuroticism (Lahey, 2009). Perceptions of own performance are another form of negative self-reflection also associated with pathology in mood disorders (Fu et al., 2005). This chapter firstly aims to outline neuroticism and negative self-reflection, in the form of self-criticism and perceptions of own performance, across GAD, MDD and co-morbid history of both disorders. Chapter 6 additionally pilots a of a novel adaptation of a tool designed in the 1960s to measure perceptions of performance in school children (Nuttin & Greenwald, 1968), recreated here as the

Fake IQ Task (FIQT). Given the potential issues with over reliance of self-report measures of self-reflection, this tool aims to reduce the globalised negative self-reflection usually achieved by traditional methods and to avoid a number of potential confounds identified in current self-reflection tools. The simplistic and engaging design of this tool was chosen as it could hold promise for use in varied paradigms and in participant groups with less reliable autobiographical recall such as young children; this makes piloting across a range of disorders particularly valuable.

1.1.6.5 Chapter 7

The final chapter of this thesis indicates potential new directions for our understanding of neuroticism as a transdiagnostic factor. Moving beyond mood and anxiety disorders, chapter 7 explores how different levels of neuroticism relates to expression of the vulnerable dark triad (VDT; Miller, Dir, et al., 2010) in a group of healthy individuals. Initially, this is to clarify suggestions in the literature that the ‘core’ of the VDT is neuroticism (Miller, Dir, et al., 2010; Miller et al., 2017; O’Boyle et al., 2015). Further, as most of the previous work in this area has looked at neuroticism in relation to either composite scores of each construct or an overall VDT score, this chapter instead also breaks the constructs down in to the core components of the VDT (interpersonal antagonism and emotional instability; Miller, Dir, et al., 2010) to assess whether neuroticism has a differential effect on expression of these factors. This aims to provide information about the relationship between neuroticism and aspects of the VDT, which may have applicability to how we understand expression of neuroticism via lower-order mechanisms more broadly.

Chapter 2: General methodology

2.1 Overview of studies

This thesis incorporates four experimental studies, exploring the role of neuroticism in major depressive disorder (MDD), generalized anxiety disorder (GAD), self-perception and the vulnerable dark triad (VDT). This thesis also includes a systematic review with a small meta-analysis, the methodology for which is not outlined here, but instead is in that chapter. Table 1 indicates the chapter in which each study can be located.

Table 1

Outline of study location within thesis chapters

Study	Chapter
1	3
2	5
3	6
4	7

2.1.1 Study 1

Experiment 1: An initial experiment collecting gender and self-report big-5 personality (openness to experience, conscientiousness, extraversion, agreeableness and neuroticism) construct scores, to form a population average.

Experiment 2: A pilot study trialling the use of an online personality questionnaire to identify individuals with high neuroticism, with the aim of improving identification of candidates for recruitment to a phase II clinical trial of a novel anxiolytic.

2.1.2 Study 2

A functional magnetic resonance imaging (fMRI) exploration of the effects of anxiolytics on behavioural and neural response to threatening and goal-conflicting situations in participants with high neuroticism levels meeting the criteria for GAD.

2.1.3 Study 3

A study analysing the role of neuroticism and self-perception in expression of self-critical attitude in individuals with experience of GAD, MDD or co-morbid history of both conditions (dual) relative to healthy controls.

2.1.4 Study 4

An examination of neuroticism as the potential ‘core’ of the VDT. Individual differences in anxiety, self-critical attitude, self-perception and neuroticism were assessed in relation to symptom expression in the three constructs of the VDT: vulnerable narcissism, borderline personality disorder traits (BPD) and secondary psychopathy.

2.2 Participant inclusion and exclusion criteria

2.2.1 Study 1

Experiment 1: Male and female participants aged 18-99 with fluent English and access to the internet were recruited in Swansea (UK) via internal circulars (Swansea University research circulars) and public websites (Gumtree, www.gumtree.co.uk; Facebook, www.facebook.com).

Experiment 2: Male and female right-handed participants aged 18-50 in the Greater London area with fluent English and access to the internet were eligible to take part. The study was advertised both internally (via the King’s College London research circulars) and externally on public-access websites Facebook (www.facebook.com), Gumtree (www.gumtree.co.uk) and Call for Participants (www.callforparticipants.com).

2.2.2 *Study 2*

Participants scoring 1 standard deviation higher than average (score of ≥ 64 for females, ≥ 58 for males) on trait neuroticism in study 1 were invited to take part in study 2.

Through telephone and in-person medical screening appointments, 28 individuals meeting the criteria for inclusion were identified. Inclusion criteria were: DSM-IV (American Psychiatric Association, 2013a) GAD diagnosis, as assessed by the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998), fluent English and able to undergo fMRI scanning procedures (e.g. no permanent metal in body, no significant claustrophobia). Participants were excluded if they were co-morbidly depressed (score of ≥ 15 on the Montgomery-Åsberg Depression Rating Scale; MADRS; Montgomery & Asberg, 1979) or had any additional psychiatric diagnoses beyond GAD (except for social anxiety, which was a permitted co-morbidity), had untreated cardiovascular, renal, immunological or hepatological disorders, had smoked within the last three months, had neurological disorders or learning disabilities, or had uncorrected visual problems.

2.2.3 *Study 3*

Male and female individuals aged 18-99, with fluent English and access to the internet were eligible to take part.

2.2.4 *Study 4*

Male and female individuals with a neuroticism score of 1 standard deviation above (score of ≥ 64 for females, ≥ 58 for males) or below (≤ 32 for females, ≤ 26 for males) average (as defined in study 1) as measured in study 3 (see study design section, below) and able to travel to King's College London were eligible to take part in study 4.

2.3 Ethical approval

2.3.1 Studies 1 & 2

Ethical approval was granted by the South London and Maudsley NHS Trust and King's College London boards (REC committee number 14/LO/2127) and Swansea University ethics board (note: the data from Swansea was not collected as part of this thesis). All participants provided written informed consent.

2.3.2 Studies 3 & 4

Ethical approval was granted by King's College London (RESCMR-16/17-4080). All participants provided separate written informed consent for the two studies.

2.4 Study design

Study materials are outlined within each chapter.

2.4.1 Study 1

Experiment 1: the first experiment was conducted online using a specialised portal (www.measureyourpersonality.com) created by Psyal (www.psyal.co.uk). Participants completed a measure of the big-5 personality traits (openness, conscientiousness, extraversion, agreeableness and neuroticism) and a series of demographic (age, gender, location) questions. Average neuroticism scores were calculated for male and female identifying participants.

Experiment 2: This experiment was also initially conducted online using the same platform as experiment 1. In addition to the self-report big-5 personality measure and demographic questions, participants answered items regarding fMRI scanner safety (e.g. presence of unremovable metal in body, significant claustrophobia) and core exclusion criteria (e.g. history of smoking). Following completion, those scoring one standard deviation above the average on neuroticism (as defined in experiment 1) received an invite to contact the research team if interested in taking part in the clinical trial. These individuals then underwent telephone screening and if appropriate full

medical screening for inclusion. All participants, regardless of neuroticism score, received an automated personality profile via email (see appendices for example).

2.4.2 *Study 2*

Study 2 was a randomised four-way crossover double-blind trial. Participants attended 6 study appointments, receiving the medication in a randomised order across 4 main visits. During the visits, participants provided self-report anxiety and dread data, and completed an active measure of defensive behaviour in the MRI scanner. Self-report big-5 personality scores were available from study 1, with the permission of the participants.

Participants were screened by a psychiatrist and excluded based on presence of physical health conditions (for example, diabetes or diseases of the vital organs) or additional mental health disorders (though co-morbid social anxiety was permitted). Participants were excluded if they scored ≥ 15 on the Montgomery-Åsberg Depression Rating Scale (MADRS; Montgomery & Åsberg, 1979) to minimise presence of co-morbid depression in the sample. Participants were excluded if they were currently taking any psychotropic medication, any investigational products or any prescribed drug that is a potential cytochrome P450 3A4 inducer (e.g. carbamazepine, phenobarbital, rifabutin, rifampin) within the previous 30 days. Use of any prescription or over-the-counter medication within less than 5 times the elimination half-life before first dose. Participants were excluded if they had smoked within last three months, and were required to have no uncorrected visual problems, neurological disorders or learning disabilities, and to have fluent English.

Participants received one of the three active doses or a placebo at each visit (4 intervention visits in total). The novel anxiolytic (BNC210) was administered at high (2000mg) and low (300mg) doses in liquid form, and lorazepam at 1.5mg in pill form. See Figure 1 for dosing schedule. As the absorption rates of BNC210 and lorazepam differ, the dosing schedule and placebo administration was manipulated by incorporating two dose administrations per visit to maintain

the double-blind. The placebo also varied in consistency (liquid or pill capsule) to preserve the double-blind.

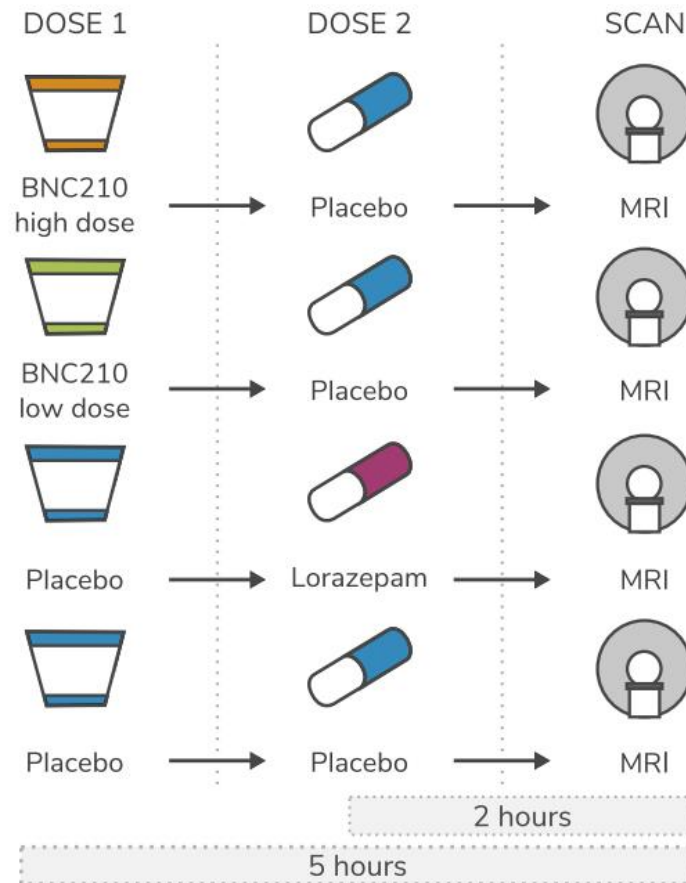


Figure 1 Dosing schedule procedure for the four pharmaceutical interventions (placebo, lorazepam, BNC210 high dose and BNC210 low dose). Time along bottom of image indicates time from dosing to MRI scan initiation.

2.4.2.1 Scanning procedure:

Data was acquired using a GE MR750 3-Tesla MRI scanner with a 12-channel head coil, in the Clinical Research Facility at King's College Hospital. Each functional run collected 180 volumes, following a T2*-weighted echo-planar imaging sequence (TR = 2000, TE = 30ms, FOV = 22.1cm, 41 slices at a spatial resolution of 3.3mm³). To allow magnetisation equilibration, the initial 4 volumes were discarded. Volumes were acquired sequentially (top-to-bottom). We also acquired

high-resolution T1-weighted structural scans (TR = 7.31, TE = 3.02, 196 slices with voxel size 1.2 x 1.05 x 1.05mm) for each participant.

Due to the absorption rate of BNC210 scanning took place 5 hours after first dose. As lorazepam has a shorter absorption rate of 2 hours, multiple doses per visit were conducted to help maintain the double-blind (only 1 active dose per visit; see figure 1). The JORT measure was the last in a sequence of behavioural tasks (not discussed in this thesis), taking place about 1 hour in to the scan. During the first (screening) visit, participants underwent a mock scanning session to expose them to the equipment and noises experienced during a typical scan. This was done to minimise anxiety and claustrophobia during the actual scan sessions.

2.4.3 Study 3

Participants gave demographic information (age, gender) and recorded any diagnosis of mental health conditions (unlimited selection from a list of GAD, MDD and other psychiatric conditions, with the option to report 'no diagnosis'). They then completed self-report measures of the big-5 personality traits, self-criticism and a novel measure of perception of (own) performance online (in the described order). Participants received an automated personalised personality break-down via email following completion of the experiment.

2.4.4 Study 4

Participants identified from those completing study 3 (due to neuroticism scores of 1 standard deviation above or below the gender average, as defined in study 1) were invited to attend a session onsite at the Institute of Psychiatry, Psychology and Neuroscience. Participants completed three measures of the VDT; self-criticism, perception of performance personality data was available from study 3 with the consent of the participants.

2.5 Statistical analysis

Questionnaire data for all studies was analysed using SPSS version 23.0 and 24.0 (SPSS Inc., Chicago, US.). The behavioural data from study 2 was also analysed using this program. The structural equation modelling in study 3 was conducted using AMOS (SPSS Inc., Chicago, US.). fMRI analysis in study 2 was conducted using the Statistical Parametric Mapping (SPM12) software and customised Matlab scripts developed by Dr Toby Wise. Findings were reported using Montreal Neurological Institute (MNI) standardised space.

2.6 Participants

2.6.1 Study 1

Experiment 1: A total of 2,352 individual completed experiment 1. Basic information (% female, mean age, mean neuroticism score) is shown in Table 2.

Experiment 2: A total of 6,293 individuals completed experiment 2. Table 2 provides basic information.

2.6.2 Study 2

From study 1 (experiment 2), 28 individuals were recruited to study 2 (with 4 dropping out, resulting in 24 completions). Table 2 provides basic information.

2.6.3 Study 3

Study 3 included 871 individuals, making up three groups: healthy controls ($n = 580$), generalized anxiety disorder ($n = 80$) and major depressive disorder ($n = 156$). Table 2 provides basic information.

2.6.4 Study 4

Data from 41 individuals was included in study 4. The sample was split in to high ($n = 19$) and low ($n = 22$) trait neuroticism scorers. Table 2 provides basic information.

Table 2

Basic demographic information and average neuroticism scores of participants, by study

		N	Female (%)	Age (SD)	Neuroticism (SD)
Study 1	Exp. 1	2,352	1,747 (74.3)	28.62 (11.4)	46.45 (16.1)
	Exp. 2	6,293	4,503 (71.6)	25.03 (25.8)	48.6 (15.8)
Study 2		24	21 (87.5)	23.5 (6.5)	71.0 (5.3) *
Study 3		871	628 (77.0)	25.9 (8.4)	49.7 (15.7)
Study 4		41	29 (70.7)	24.6 (5.7)	High: 70.6 (5.7) *
					Low: 24.6 (5.3) *

* Sample selected for specific neuroticism scores, average not representative of general population

Data is mean score and (standard deviation) unless specified otherwise.

Chapter 3: Neuroticism as a tool for the identification of candidates for clinical trials in psychiatric research

3.1 Chapter Summary

The cost of a clinical trial is impacted by participant recruitment efficacy and success. The creation of a pre-screening method that identifies appropriate candidates for full medical and psychiatric screening would be desirable to minimise inconvenience and cost to both the trial staff and volunteers, and additionally to facilitate identification of treatment-free individuals who may not be in touch with clinical services. Non-invasive transdiagnostic mechanisms, such as neuroticism, are candidates for broad-scale identification of individuals meeting the criteria of mood and anxiety disorders. This study explores a potential online pre-screening tool for this purpose. The Trait Self-Description Inventory (TSDI) is a measure of the big-5 personality traits of openness to experience, conscientiousness, extraversion, agreeableness and neuroticism. As discussed in the introductory chapter of this thesis, high neuroticism is frequently associated with presence of mood and anxiety disorders and is therefore considered a candidate transdiagnostic mechanisms common across these diagnoses. As such, online self-report of neuroticism may be a non-invasive and broad-scale method of identifying candidates for recruitment to research investigating mood and anxiety disorders. The first aim in this chapter was to analyse the properties of the TSDI neuroticism scale in a general population sample, and to explore the ability of scores on this measure to identify individuals with psychiatric diagnoses. Results from a receiver operating characteristic (ROC) analysis indicated that the neuroticism scale of the TSDI has good ability to discriminate those with a psychiatric diagnosis of major depressive disorder (MDD) and generalized anxiety disorder (GAD) from never-diagnosed individuals.

Following the success of the first stage, the online TSDI personality measure was adapted for use as a recruitment tool in clinical trials. The initial pilot study, presented here, developed the tool to screen for the trial's basic criteria. Primarily, the neuroticism scale was utilized to identify candidates with a higher chance of meeting the criteria for GAD. The online platform screened

6,293 people in one year. A total of 862 eligible individuals were identified through this route, each of whom automatically received an email invitation to contact the study team for further telephone screening. Of those, 266 individuals contacted the team and 173 were telephone screened, with 53 attending the study site for medical checks. Twenty-eight individuals were fully eligible, and 24 completed the trial. This permitted completion on time and on budget.

Our online pre-screening personality questionnaire platform did not remove the need for telephone screening or on-site medical checks but did increase the efficiency of recruitment through non-invasive identification of those meeting key requirements. Thus, our platform is a useful recruitment technique for clinical trials and is time-saving for both the trial and potential participants. Additionally, the results presented here are supportive of neuroticism as a key transdiagnostic mechanism in GAD and MDD.

This chapter expands upon an article published in the journal of Neuropsychiatric Disease and Treatment (Patrick et al., 2018) of which I am first author. The published manuscript can be found in the appendices.

3.2 Introduction

Recruitment is integral to clinical trials (Borschmann et al., 2014; Rojavin, 2005). However, both under-recruitment and protracted recruitment periods are a persistent issue (Borschmann et al., 2014; McDonald et al., 2006). Failure to meet recruitment targets is one of the most frequent reasons for early trial termination (Kasenda et al., 2014; Sullivan, 2004). Discontinuation or extension of trials is not only costly (Kopcke & Prokosch, 2014; Sullivan, 2004) but can also impact the validity and reliability of study results (McDonald et al., 2006; Patterson, Kramo, Soteriou, & Crawford, 2010). Improving recruitment is vital to maintaining evidence-based medicine and gold-standard research.

Problems identifying eligible candidates and obstacles to recruitment via clinical services are a particular concern (Wise et al., 2016), especially within vulnerable populations (Howard, de Salis, Tomlin, Thornicroft, & Donovan, 2009; Patterson et al., 2010). Recruitment via clinical services

is a traditional approach, but a host of limiting factors have been highlighted (Wise et al., 2016). This route typically requires referrals from gatekeepers; however the time pressure gatekeepers are already under (Borschmann et al., 2014; Sullivan, 2004; Wise et al., 2016) and concerns around referral to research impacting the therapeutic relationship (Borschmann et al., 2014; Howard et al., 2009) limit the efficacy and success of this approach. Secondary and tertiary services tend to see more complex cases with greater co-morbidity of diagnoses (Keown, Holloway, & Kuipers, 2002), meaning that trial volunteers who are treatment-free, treatment-naïve or highly prototypical are less likely to be identified via these common means of recruitment (Wise et al., 2016). This can severely limit recruitment to early-stage disease-mechanism trials and initial-phase clinical trials, which often require treatment-free participants without secondary diagnoses.

Several potential alternatives have been explored, with varied success. E-mail and online media distribution have proven effective in maximising interest (Kirkby, Wilson, Calvert, & Draper, 2011; Montag, Reuter, Jurkiewicz, Markett, & Panksepp, 2014). Online advertisement has been particularly successful, outperforming recruitment via clinical services (Wise et al., 2016). Improved broadcasting of research opportunities is progressive, as not only is the range of candidates accessed widened, but candidate autonomy is improved, and gatekeeper time investment is reduced. However, screening the individuals responding to online advertisements still requires considerable time investment from researchers (Wise et al., 2016), often for little recruitment pay-out. Considering the time-sensitivity of clinical trials which often have fixed end dates, researcher time investment is a key concern. E-screening methods have been proposed, using clinical database searches within clinical facilities; though these are efficient in removing ineligible candidates (Thadani, Weng, Bigger, Ennever, & Wajngurt, 2009), they are dependent on participants having had previous contact with clinical services, which could limit identification of treatment-naïve individuals. Mail-based pre-screening drives, where participants complete and return postal questionnaires, have been successful in specific patient populations (Andersen et al., 2010). Combining a pre-screening stage with online recruitment could be a huge boon to research.

A potential new method of recruitment was developed for use in the Anxiety-Related Personality Traits (APT) trial, which was a functional Magnetic Resonance Imaging (fMRI) trial of a novel anxiolytic drug. The APT trial was a Phase IIa randomised controlled trial (RCT), recruiting treatment-free individuals meeting the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) criteria for GAD without co-morbid MDD. The study criteria was predicted to be difficult to fulfil through traditional routes, as GAD typically has high rates of co-morbidity (Takahashi et al., 2015) and there is commonly an under-representation of treatment-free individuals in care services (Keown et al., 2002). This was compounded by the relatively tight time frame for recruitment. As online pre-screening is remote and doesn't necessarily lead to enrolment in research, care should be taken that the process is minimally invasive for the participant population, whilst collecting suitable breadth of information. Therefore, in order to identify highly anxious individuals a non-clinical personality questionnaire was chosen. The TSDI (Collis & Elshaw, 1998) is a 172 item self-report questionnaire measuring the Big-5 personality traits of openness (to experience), conscientiousness, extraversion, agreeableness and neuroticism. The literature shows strong associations between high scores on the personality trait of neuroticism and experience of and diagnosis of anxiety disorders such as GAD (Barlow, Sauer-Zavala, Carl, Bullis, & Ellard, 2014; Lahey, 2009), with departures of only one standard deviation (SD) from the average score associated with increased risk (Lahey, 2009). Accordingly, we used the TSDI as a pre-screening measure to identify individuals who possessed high neuroticism scores ($1 \text{ SD} \geq \text{mean}$) and were thus more likely to be suitable for the APT trial.

3.2.1 Aims & hypotheses

This study was formed of two experimental stages. Experiment 1 administered the 50-item TSDI online to two general population samples. The first sample was used to generate average, standard deviation and reliability scores for the tool. The second sample was used to assess the sensitivity and specificity of the neuroticism trait scale for identification of those with a self-reported psychiatric diagnosis.

Experiment 2 aimed to pilot the use of an online pre-screening tool for use in recruitment to clinical trials. Cut-off scores identified in experiment 1 were applied to the online TSDI in experiment 2 to identify those most likely to meet eligibility criteria for the APT trial. Individuals responding to the APT trial advert completed the online screening tool as a first step in the recruitment process.

3.3 Experiment 1

3.3.1 Methods

3.3.1.1 Participants

This stage was advertised in two data collection periods, firstly advertised through Swansea University email circulars (sample 1), and the second through King's College London email circulars and public-access websites (Gumtree.co.uk, Callforparticipants.com; sample 2). Participants completed the online 50-item TSDI; participants recruited in the second sample also reported their psychiatric diagnostic history and completed several additional online questionnaires (latter not reported here but explored in chapter 6). No eligibility criteria beyond access to the internet, being aged 18-99 and having fluent English were applied. Further details can be found in chapter 2.

3.3.1.2 Materials

The Trait Self-Description Inventory (TSDI; Collis & Elshaw, 1998). A 50-item self-report version of the original (172-item) TSDI, adapted for online use. The tool measures the big-5 personality traits of openness (to experience), conscientiousness, extraversion, agreeableness and neuroticism. Participants respond to a series of questions and adjectives, using a Likert scale response system.

3.3.2 Analysis

SPSS (IBM Inc., Chicago) was used to assess average scores and standard deviation for each trait measure of the TSDI, and using a separate sample, applied a ROC curve to establish sensitivity

and specificity of the neuroticism trait scale in identifying those with previous psychiatric diagnoses.

3.3.3 Results

Sample 1 consisted of 2,532 complete data sets (after data cleaning; 74.3% female). Average trait scores and standard deviations are indicated in Table 3.

	<u>Male</u>		<u>Female</u>		<u>Combined</u>	
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
Openness	42.09	12.65	39.31	11.90	40.17	12.21
Conscientiousness	47.97	11.40	49.34	11.26	48.92	11.32
Extraversion	-2.99	13.46	.40	13.68	-.65	13.70
Agreeableness	42.34	11.40	46.91	10.42	45.49	10.94
Neuroticism	42.10	15.63	48.40	15.90	46.45	16.08
Age	27.82	11.52	28.99	11.26	28.63	11.35

SD, standard deviation; TSDI, Trait Self-Description Inventory, M, mean.
N = 2,352 (1,747 female)

Average score and standard deviation were used to calculate a high neuroticism cut-off. As a significant different in neuroticism score was shown between genders ($p < .001$), these were different for female (score of 64; $48.40 + 15.90$) and male (score of 58; $42.10 + 15.63$) populations.

A ROC analysis was then conducted on a second, independent sample ($n = 871$; 588 healthy controls) to assess the ability of trait neuroticism score to identify individuals with psychiatric diagnosis. ROC output suggested that the neuroticism trait score some ability to identify those reporting a previous psychiatric diagnosis (area under curve (AUC) = .590, confidence interval: .551 - .630, $p < .001$). Following, the analysis was repeated for those reporting a GAD diagnosis specifically, for which neuroticism was a slightly stronger identifier (AUC = .695, confidence

interval: .637 - .753, $p < .001$), and MDD (AUC = .671, confidence interval: .625 - .717, $p < .001$).

Figure 2 shows the ROC graph outputs for GAD and MDD diagnosis presence.

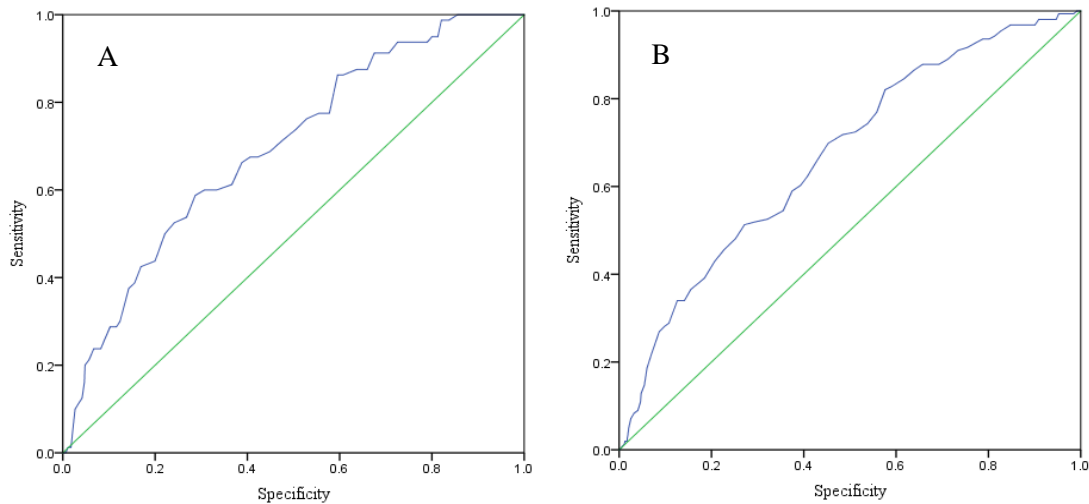


Figure 2 ROC graphs of trait neuroticism as an indicator of a) GAD diagnosis presence, and B) MDD diagnosis presence.

In this sample, self-reported prevalence of MDD and GAD was 19.3% and 10.7% respectively. Positive predictive value (PPV) and negative predictive value (NPV) were calculated to further explore the value of this measure. PPV for individuals with (self-reported) MDD and/or GAD ($n = 160$) diagnosis was 39.4%; NPV of those with MDD and/or GAD was 81.6%.

3.4 Experiment 2

3.4.1 Methods

3.4.1.1 Participants

Potential candidates for the APT trial advert accessed the online pre-screening tool via a web-portal created by Psyal.co.uk (Psyal, London, UK; www.measureyourpersonality.com). The tool determined initial eligibility through trait neuroticism scores of ≥ 1 standard deviation above the mean (determined as 58 and 64 for male and female candidates respectively, according to average and standard deviation scores obtained in experiment 1), MRI scanner compatibility (i.e. no metal

in the body/eyes, no self-reported claustrophobia), location (restricted to Greater London) and basic trial requirements (i.e. non-smoking, aged 18-50).

The APT trial consisted of a repeated-measures within-subjects design with four MRI dosing visits separated by a washout period and had strict inclusion criteria. It required 24 participants aged 18-50 who met the criteria for, though were not necessarily diagnosed with, GAD as outlined by the MINI (Sheehan et al., 1998) and were not currently under any treatment program (pharmacological or psychological) for their anxiety. Individuals were not eligible if symptoms of MDD were present, i.e., required a score of <15 on the Montgomery-Åsberg Depression Rating Scale, MADRS (Montgomery & Asberg, 1979), and needed to be able to undergo MRI procedures. Other psychiatric disorders (except for social phobia), any significant cardiovascular, gastrointestinal, hepatic, renal, respiratory, endocrine, immunologic or haematological disease, current use of any prescription or over-the-counter medication (with the exception of contraceptives), or smoking (current or within last 3 months) were exclusion criteria. If recruited to the APT trial, participants would be paid for their time. Participants were recruited from the general public and university staff/students across the Greater London area between June 2015 and June 2016.

Ethics was granted by NRES Committee Chelsea, London (14/LO/2127); all participants provided written informed consent to the online pre-screening tool on the web portal and written informed consent in person to all medical screening visits and enrolment.

3.4.1.2 Design

As traditional recruitment via clinical services was not expected to be highly effective, the pre-screening questionnaire was instead advertised in the general population. After completion of the online pre-screening session, the portal generated an individually tailored personality profile which was emailed to all participants automatically by the website algorithm. The individualised feedback was designed to be engaging and to promote participation in this stage of the project, without resorting to typical (and costly) methods of enticement (e.g. voucher/prize raffles). The

questionnaire was disseminated via online advertising across both public (Gumtree, CallforParticipants, Facebook) and institutional (King's College London and partners website and email circulars) platforms.

If the respondent met the pre-defined criteria (i.e., neuroticism score ≥ 64 for females, ≥ 58 for males, MRI compatible etc.) their automated email also contained the APT trial information sheet and a message inviting them to contact the research team. The individuals who then initiated contact were telephone screened by the research team to check eligibility in greater detail. Those eligible at the telephone screening stage were invited to attend on-site medical screening. This method aimed to not only minimise researcher time spent on participant identification and pre-screening, but to also minimise unsuccessful and unnecessary in-person medical screening visits. Contact was in the control of the candidates to minimise impact on candidates. The researchers received a copy of the emails sent to eligible individuals which allowed them to track numbers.

3.4.2 Analysis

Analysis in experiment 2 comprised descriptive statistics and was performed using SPSS (IBM Corp). A CONSORT flowchart tracked participant progress.

3.4.3 Results

A total of 6,293 individuals completed the online personality questionnaire (after removal of duplicates). The pre-screening algorithm identified 862 eligible candidates who received the additional study information and contact details. Of these, 266 contacted the research team and 173 participated in telephone-screening. Telephone-screening established that 53 of these candidates were eligible for medical screening at the clinical site; the other 120 were excluded at this stage based on factors such as availability, current medications schedules and physical health concerns. At the on-site medical screen, study physicians excluded 25 of the 53 potential participants (due to exclusion criteria not possible to identify during the telephone screening process, for example blood test abnormalities; 12 of the exclusions at this stage were due to MADRS scores of >15 , as per protocol exclusion guidelines), resulting in 28 enrolments. Four

candidates later withdrew (due to: scanner breakdown, $n = 1$, time constraints, $n = 2$; non-adherence to study guidelines, $n = 1$), resulting in the APT trial completing on time and on budget; see Figure 3 for a CONSORT flowchart of participant progress through the trial.

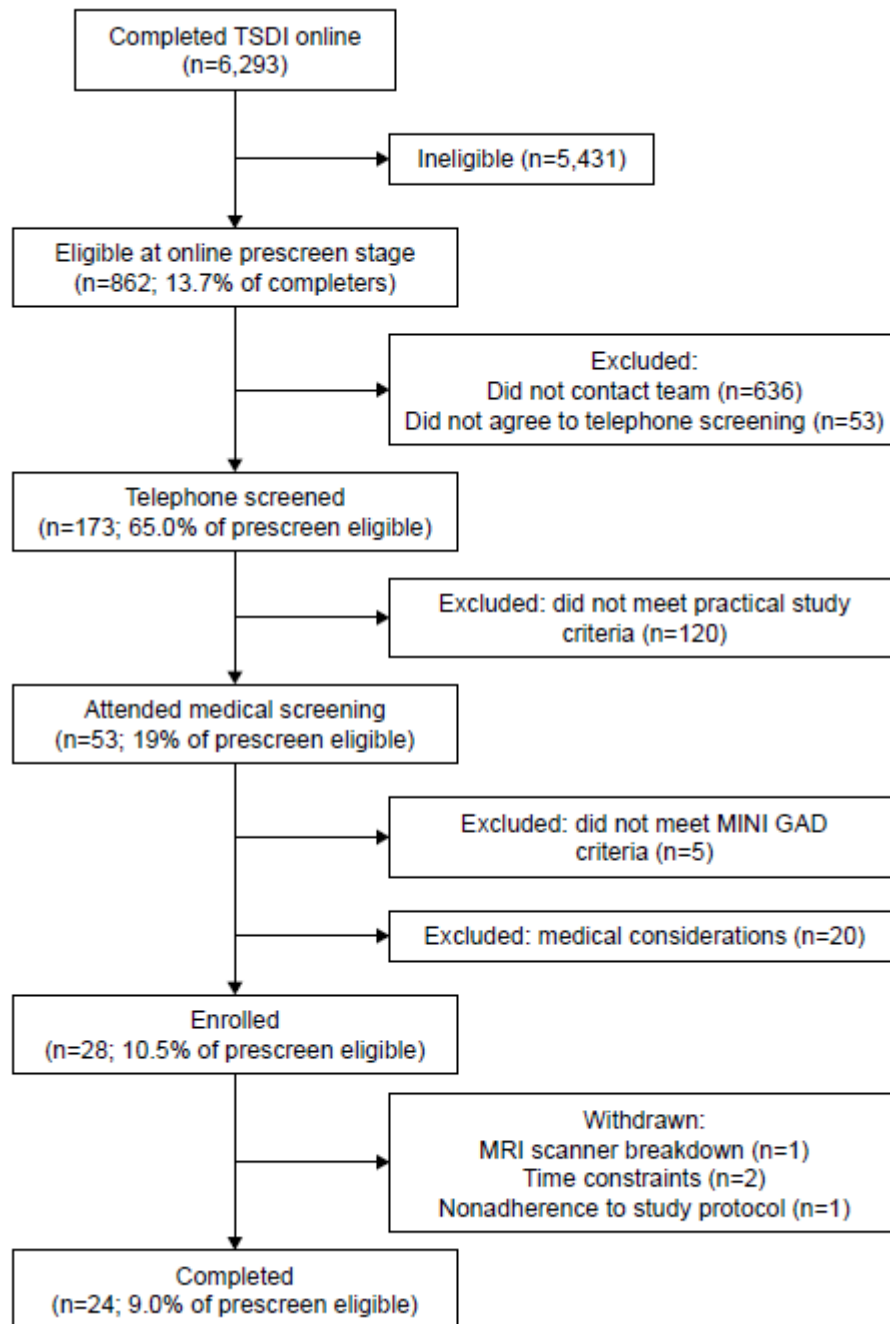


Figure 3 CONSORT diagram of participant progress through APT trial

Recruitment was paused whenever 24 candidate positions were filled, to prevent unnecessary medical checks for individuals who may not end up being fully enrolled. Table 4 indicates the gender and age data at each stage of the recruitment process.

Table 4			
Average (mean) age and gender of sample at different recruitment stages of APT trial			
	Mean age (range)	Female (%)	N
Completed online pre-screen	25.03 (18-50)	4,503 (71.6)	6,293
Telephone screened	23.22 (18-50) *	120 (70.2) *	173
Attended medical screening	22.98 (18-49)	41 (77.4)	53
Completed trial	23.54 (19-49)	21 (87.5)	24
* 14 missing data items			

Table 5 shows average score and internal consistency for each personality trait.

Table 5		
Average (mean) scores and reliability alpha scores for personality traits		
	Mean score (SD)	Cronbach's alpha
Openness	45.4 (11.6)	.826
Conscientiousness	50.1 (11.0)	.875
Extraversion	-2.2 (13.9)	.924
Agreeableness	47.3 (9.8)	.894
Neuroticism	48.6 (15.8)	.905
SD, standard deviation		

3.5 Discussion

Recruitment using our online pre-screening method generated a large response rate, permitting successful recruitment of a full cohort of hard-to-identify participants within a restricted time frame. Use of trait neuroticism as measured by the online 50-item TSDI is supported by analysis suggesting this factor has slight predictive ability to discriminate those likely to have/fit a GAD diagnosis, relative to those reporting no mental health conditions. Though the PPV was not high, there may be an issue in understanding disease prevalence in this sample due to the reliance on self-reported diagnosis. This may limit confidence in this tool as currently assessed as an identifier, and as such further work in a clinically defined sample is required. Similarly, the percentage of individuals with MDD and/or GAD in the sample population was relatively small (18%), which some suggest may be a limiter in the accuracy of identifier tests such as PPV (F. Chen, Yang, & Chen, 2013; Vecchio, 1966). NPV was high, suggesting it may also be of interest to explore neuroticism as a tool for identifying those at low risk of GAD and/or MDD.

Despite this, as only 31% of RCT studies achieve recruitment success and 54% require grant extensions in order to fulfil targets (McDonald et al., 2006), the recruitment method developed here has some promise. This method combines the efficiency and economic benefits of online advertisement (for example, Wise et al., 2016) with online pre-screening to accelerate recruitment and reduce time demands on study personnel. Research has suggested word-of-mouth is key, particularly in non-financially incentivised recruitment (Luzurier et al., 2015), indicating the importance of a tool with engaging feedback such as a personality measure in promoting engagement. Recent initiatives recommend the use of digital technology to generate research data and study populations (Department of Health and Social Care, 2017), suggesting development of an online pre-screening method is timely.

Of the volunteers invited to medical screening on-site only 9.3% did not meet the main psychiatric eligibility criteria (presence of GAD), indicating the accuracy of our pre-screening method. In addition to the considerable issues in recruitment of treatment-naïve participants generally, recruitment of GAD patients without co-morbid MDD can be especially difficult due to the high

levels of co-morbidity between these conditions (Takahashi et al., 2015). Timely recruitment of an adherent sample as shown here indicates the success of this method in identifying a minority population. Considering the cost of medical screening (e.g. psychiatrist time, blood sample processing, transport expenses for the participant etc.) and the time-sensitivity of clinical trials, our method helped greatly reduce unnecessary on-site medical screening visits. Further, this methodology aimed to reduce pressure on gatekeepers elicited by traditional routes of recruitment via clinical services, and could also increase patient autonomy in research involvement (Howard et al., 2009), widening research participation.

Research has highlighted trans-diagnostic factors within mental health pathology, positing common underlying traits which contribute to the development and maintenance of mood and anxiety disorders (Barlow et al., 2014; Griffith et al., 2010; Krueger, Chentsova-Dutton, Markon, Goldberg, & Ormel, 2003; Rodriguez-Seijas, Eaton, & Krueger, 2015). Variations in trait strength or in the combination of underlying constructs within traits may influence the symptom profile of different disorders (Barlow et al., 2014). As our ROC analysis suggested neuroticism was also a potential predictor of MDD diagnostic presence, future work should expand the conditions catered for by this methodology. The results presented here support neuroticism as a high-level factor in GAD; this contributes to work investigating neuroticism as a candidate transdiagnostic factor in mood and anxiety disorders (Barlow et al., 2014; Gray, 1982; Griffith et al., 2010), suspected due to high level of co-morbidity (Krueger et al., 2003; Rodriguez-Seijas et al., 2015), broad treatment response (Bakker et al., 2002; Bandelow et al., 2015; Norton, 2012) and common neurobiological function (Barlow et al., 2014). Recruitment via constructs such as neuroticism is a therefore logical step, as work has already suggested diagnostic frameworks in a similar vein to the recruitment paradigm outlined here (Rodriguez-Seijas et al., 2015). Development of this or similar tools could provide a cost- and time- efficient method of recruitment to clinical trials; such improvements to recruitment methodologies could in turn reduce early termination and discontinuation of trials, which is often associated with poor participant identification in practice (Kasenda et al., 2014; Sullivan, 2004).

3.6 Limitations & future directions

Though using neuroticism scores to identify those likely to experience anxiety is in line with the literature (Lahey, 2009), further work is required to fully refine this process and ensure broad recruitment to trials is maintained. Though neuroticism is highly associated with conditions such as GAD, any individuals experiencing GAD without high neuroticism should not be ignored. As with any online tool, care must be taken to ensure a wide range of demographics are represented and internet access is not a limiter (Wise et al., 2016). A large proportion of candidates completing the online pre-screen were female, though as anxiety disorders are more common in women than men (Kessler et al., 2005) this skew may be specific to the target disorder.

In light of these points, the presented methodology is proposed as a supplement to traditional modes of recruitment with particular utility as a means of recruiting treatment-free prototypical participants who are not in touch with clinical services. Neuroticism has been linked to other mental and physical health disorders (Lahey, 2009; Malouff et al., 2005), suggesting our method could be used to identify candidate participants with a broad range of conditions. Moreover, other personality traits have been tied to psychopathology, such as high and low levels of extraversion being linked to conduct disorders and mood disorders respectively (Malouff et al., 2005). This indicates potential for tailoring of the personality criteria of the online platform to enrich recruitment populations in a multi-dimensional manner by, for example, selecting individuals who score high on neuroticism but low on extraversion. Some caution should be taken in regard to the analysis of neuroticism's ability to determine psychiatric conditions presented here, as psychiatric diagnoses were self-report by the participants themselves only. Validation of this concept with clinical scales of psychiatric disease, rather than self-report of its presence, would be beneficial. Further, this study was cross-sectional in design, and as such no comment on the use of neuroticism for prediction of later GAD diagnosis is possible.

This project was exploratory, and though the findings are promising, future work should compare this recruitment plan with traditional clinical services routes for full assessment of efficacy and analysis of patient groups recruited via each channel. Analysis of the financial cost of this

methodology would also be informative. Development of a wider screening process using this methodology to recruit to a range of trials alongside clinical service-based recruitment is currently underway. Future projects should ensure the ethical considerations behind using trait characteristics as identifiers in health are given due weight, and would benefit from developing community engagement relationships with target populations to ensure relevance and diverse representation is achieved (Hood, Brewer, Jackson, & Wewers, 2010).

3.7 Conclusion

In conclusion, the online pre-screening personality questionnaire created for the APT study allowed automatic screening of thousands of people for high scores on neuroticism, plus the study's basic screening requirements (in this case MRI safe, living in or near London, right-handed, non-smokers, aged between 18 and 50). Though our new method does not obviate the need for telephone screening or on-site medical checks, it does make these steps quicker and cheaper than usual and aims to minimise impact on candidate participants. There is strong promise for application of this tool beyond GAD, particularly in to the broader mood and anxiety disorders category. Thus, the online pre-screening personality questionnaire approach is a useful tool for recruiting clinical trial participants, as it is not only potentially cost-saving, but also time- saving for both candidates and trial staff, whilst aiming to be of interest to the candidate population. The results of experiment 1 support the use of transdiagnostic mechanisms for recruitment of treatment-naïve or currently treatment-free individuals to clinical trials in MDD and GAD.

Chapter 4: Brain activation during human defensive behaviour- a systematic review and preliminary meta-analysis

4.1 Chapter summary

Aberrant defensive behaviour has been linked to psychopathology (Bijttebier et al., 2009); as such, the neural underpinnings of defensive behaviour have implications for both basic research and clinical translation. Neuroticism, and a more general abnormal response to negative stimuli, has been proposed as core factors underlying the functioning of defensive behaviour systems (Barlow et al., 2014; Gray, 1982; McNaughton & Corr, 2004). However, as most of the work focusing on active defensive behaviour (as opposed to self-report measures) to date has focused on animal models (Kirlic et al., 2017) the theoretical involvement of these individual differences has yet to be substantiated. This review was designed to systematically collate published research on neural response during defensive behaviour (specifically, simple avoidance of threat and approach-avoidance behaviour during goal-conflicting situations) and to present an exploratory meta-analysis of available whole-brain data, for comparison with the experimental output of chapter 5. The aim was not only to provide an overview of neural activation during human defensive behaviour, but also to review the current status of defensive behaviour paradigms and tools, and to outline the present understanding of individual differences in expression of defensive behaviour.

Scopus, PsychInfo and Web of Science databases were searched for the period up to March 2018. 1,348 simple avoidance and 1,910 goal-conflict publications were initially identified; following full text review, 8 simple avoidance and 11 goal-conflict studies were included in the systematic review. Due to issues with high heterogeneity, 5 of the 16 manuscripts included in the systematic review had datasets that were eligible for use in the meta-analysis. The systematic review identified a move from forebrain-to-midbrain activation as threat becomes more pertinent, indicating support for the Reinforcement Sensitivity Theory (RST) of behaviour (McNaughton & Corr, 2004) and general compatibility with animal work. Few studies included in the systematic

review investigated the contribution of personality or trait-level characteristics to defensive behaviour, though there were some indications that trait anxiety and neuroticism may play a role in amygdala reactivity to threat and conflict (Cunningham, Arbuckle, Jahn, Mowrer, & Abduljalil, 2011; Mobbs, Petrovic, et al., 2009). A preliminary meta-analysis did not reflect the findings of the systematic review, as no change from forebrain-to-midbrain activation with increasing threat was observed. Instead, the most consistent finding of the preliminary meta-analysis was increased activity in the frontal gyri; specifically, activation of the right middle frontal gyrus and deactivation of the left middle frontal gyrus was shown in response to threat. The incompatibility of the systematic review and meta-analysis are discussed in the context of paradigm design variation and power limitations. This chapter highlights the considerable heterogeneity in current defensive behaviour tools and the lack of research in clinically relevant populations. Few studies included measures of neuroticism or other overarching factors that may explain individual variation in defensive behaviour; the theoretical role of neuroticism and related individual differences in defensive behaviour has not yet been adequately explored.

This chapter expands upon an article published in the journal of Neuroscience and Biobehavioural Reviews, of which I am first author (Patrick et al, 2019).

4.2 Introduction

Defensive behaviour and abnormal sensitivity to threat has been linked to psychopathology (Bijttebier et al., 2009; Mitchell et al., 2007), with particular relevance to anxiety disorders (McNaughton & Corr, 2004). As such, defensive behaviour is a candidate factor for consideration within a multi-dimensional, transdiagnostic approach to psychopathological anxiety. Avoidance of threat (active movement away from threat) and approach-avoidance during goal-conflict (movements or decision making designed to collect information about a situation, or move towards reward when there is a risk of adverse event) are key aspects of human defensive behaviour (Hundt et al., 2007; McNaughton & Corr, 2004). These behaviours form systems that are considered orthogonal but functionally interdependent, forming behavioural response to threat and threat-reward conflict (Jackson, 2009; McNaughton & Corr, 2004). Hyper-activation of

defensive systems have been associated with fear (Bijttebier et al., 2009; Jackson, 2009) and anxiety (Hundt et al., 2007; Kasch et al., 2002) based pathology. Defensive behaviours are thought to show considerable individual differences (Corr, 2013); one candidate factor responsible for variation in human defensive behaviour is the personality trait of neuroticism (Barlow et al., 2014; Gray, 1982; McNaughton & Gray, 2000).

Despite the clinical relevance of defensive behaviours, to date much of the experimental work to date has used animal models (Kirlic et al., 2017). Rodent research involves a range of established avoidance/approach-avoidance tasks, from exploratory behaviour tasks such as the elevated plus maze (Pellow, Chopin, File, & Briley, 1985) to those using punishment for induction of conflict such as the Vogel conflict test (Vogel, Beer, & Clody, 1971), depicting neural activation in non-human animals (Davis, Walker, Miles, & Grillon, 2010; Grillon, Morgan, Davis, & Southwick, 1998; Kumar, Bhat, & Kumar, 2013). The rodent work has highlighted the amygdala, hippocampus (Choi & Kim, 2010; Kirlic et al., 2017; Möller et al., 1997), periaqueductal grey (PAG) and midbrain (Fanselow, 1994) in response to threat and threatening conflict. Though animal findings are comprehensive and largely consistent, replication in humans has sometimes been problematic (Blanchard, 2017; Corr, 2002). Further, the majority of in-human work has relied on self-report questionnaires about imagined defensive behaviour, or passive experience of threat. These methods are arguably poor measures of defensive response, only indirectly assessing behaviour (Kirlic et al., 2017). As such, a review of the available literature concerning defensive behaviour in humans is timely and may provide direction for future research. Further, insight in to the individual differences in human defensive behaviour would be informative and is not possible via animal work.

Reinforcement Sensitivity Theory (RST) outlines human defensive behaviour, separating simple avoidance and goal-conflict both behaviourally and clinically and predicting involvement of specific neural regions. Specifically, RST predicts change in neural activation dependent on threat intensity, progressing from cortical to subcortical regions as threat increases (McNaughton & Corr, 2004) (see Figure 4). Maladaptive avoidance of threat is characteristic of panic and phobic

disorders (Blanchard, Hynd, Minke, Minemoto, & Blanchard, 2001; McNaughton & Corr, 2004) and abnormal response to conflicting stimuli is linked to diagnoses such as generalized anxiety disorder (GAD; Bijttebier et al., 2009; Hundt et al., 2007; Kasch et al., 2002); therefore understanding of human defensive behaviour architecture is vital to diagnosis and treatment (LeDoux et al., 2017). As neuroimaging becomes increasingly prevalent and more sophisticated, development of accurate tools to understand neural correlates of behaviour is crucial. Despite simple avoidance and goal-conflict behaviour having clear clinical relevance (McNaughton & Corr, 2004; McNaughton & Gray, 2000) and being well documented in animal models (Blanchard et al., 2001; Kirlic et al., 2017; Kumar et al., 2013) with a clear human neural hypothesis (Kirlic et al., 2017; McNaughton & Corr, 2004), a systematic review or meta-analysis of the evidence regarding neural systems involved in human active defensive behaviour has not yet been conducted.

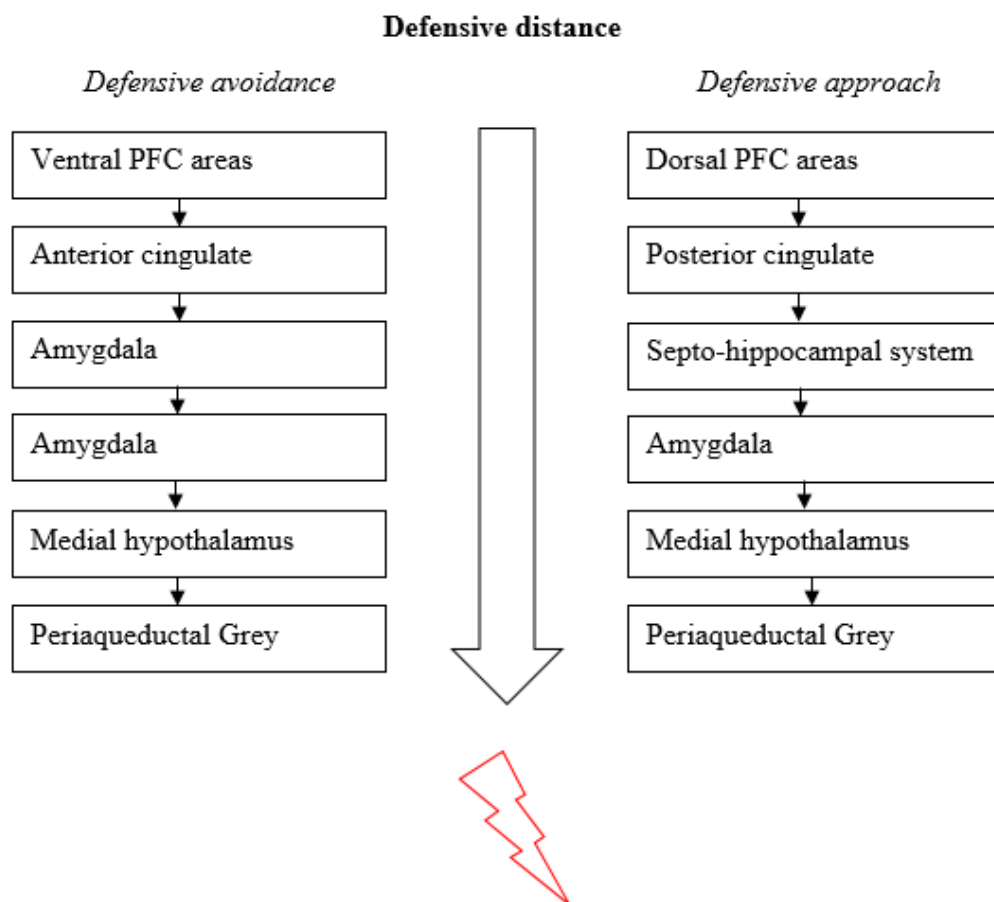


Figure 4 Neural activation during defensive behaviour under increasing threat levels, based on McNaughton & Corr (2004). Lightning bolt symbol represents threat, with threat proximity increasing from top to bottom of the diagram.

4.2.1 Aims & hypothesis

This chapter aims to explore the available human functional imaging paradigms for exploration of threat-related behaviours, and to outline the neural activation reported by individual studies. Given the clinical relevance of defensive behaviour and the paucity of a synthesized body of human translational work, the aim of this review is four-fold:

- 1) To provide an overview of neural activation via human functional magnetic resonance imaging (fMRI), Positron Emission Tomography (PET), Magnetoencephalography (MEG) or Single Positron Emission Tomography (SPECT) of active behavioural goal-conflict and simple avoidance tasks
- 2) To outline available tools and the use of physiological/self-report measures as validation of findings
- 3) To note potential roles of individual differences in RST expression
- 4) Assuming sufficient homogeneity and data, a preliminary meta-analysis of neural activation to provide additional insight.

It is expected that the neural predictions of RST, including the importance of neuroticism in expression of defensive behaviour, and the current body of animal work will be supported in this chapter.

4.3 Materials & methods

4.3.1 Literature search

Literature searches for English language papers were conducted using Scopus (Elsevier; www.scopus.com), PsychInfo (American Psychological Association; accessed via Ovid Technologies Inc, www.ovid.com), and Web of Science (Clarivate Analytics; www.webofknowledge.com). Search results were extracted March 2018, with no other date limiters. Titles and abstracts were initially assessed, with those appropriate undergoing full text review. Reference lists were manually checked for additional studies. The search terms were chosen to identify goal-conflict approach-avoid tasks and threat avoidance behavioural tools in studies using imaging techniques, excluding lesion studies. Search terms were as follows: (“threat

avoid*" OR ("threat" AND "avoid*") OR "defensive r*" OR "fight flight and freeze system" OR "fight" OR "flight" OR "freeze" OR "FFFS" OR "behavio* avoid*") AND ("*MRI" OR "SPECT" OR "PET" OR "*magnetic resonance imaging") AND ("threat" OR "predator" OR "fear" OR "anxiety").

4.3.2 *Outcome measures*

Region of Interest (ROI) data or whole-brain derived data was accepted for systematic review. To minimise bias, whole-brain data or Statistical Parametric Mapping (SPM) t-maps were required for inclusion in the preliminary meta-analysis. Articles that used a regions of interest (ROI) only, did not apply consistent statistical thresholds throughout the brain, or did not report peak coordinates in stereotactic space were excluded from the meta-analysis. The authors of work eligible for inclusion for meta-analysis were contacted requesting whole-brain or t-map data.

4.3.3 *Study selection*

Titles, authorships and abstracts were downloaded and formatted in to an excel document. Duplicates were manually removed. One author screened the titles and abstracts of all non-duplicate items, excluding the ineligible articles. Two authors assessed the eligibility of potential inclusions, reaching 100% agreement.

4.3.4 *Inclusion & exclusion criteria*

The following inclusion and exclusion criteria were applied to the studies identified by the initial literature database search.

- I. Primary studies, exploring approach-avoidance (goal-conflict) or simple avoidance active behavioural task in presence of threat/risk of threat (including physical punishment and loss of accrued prizes) through active response (including pre-programmed outcomes, providing individuals are unaware) as passive viewing of stimuli do not have direct implications for avoidance/approach (Kirlic et al., 2017).
- II. Clear description of the activation interaction presented.

- III. Written in English.
- IV. Involved adult samples (≥ 18 years of age).
- V. Samples were either healthy controls and/or anxiety diagnosed (including GAD, panic disorder, simple phobia, agoraphobia or social anxiety disorder).
- VI. Studies were excluded if they involved samples with neurodevelopmental, neurodegenerative or lesion-based conditions (though any healthy control arms could be included)
- VII. Psychiatric conditions beyond those outlined above are basis for exclusion, except for concomitant depression due to the high co-morbidity between these conditions. Studies recruiting individuals with single- or main- diagnosis of depression were not included.
- VIII. Methodology outside of fMRI, MRI, PET, MEG and SPECT will be excluded as beyond the scope of this review.

Depression was considered outside the scope of this review. There were a number of reasons for this decision: there is evidence to suggest that the association between threat sensitivity and anxiety is stronger than in depression (Naragon-Gainey, 2010), it may also be that passive avoidance is more relevant to depression (Ferster, 1973; Ottenbreit & Dobson, 2004), and though there is little research in to defensive behaviours in depression using active avoidance paradigms, a study using this approach found no significant differences in neural activation between depressed patients and healthy controls (Marwood, 2017).

4.3.5 Seed-based d Mapping (SDM) meta-analysis

SDM is a well validated (Radua et al., 2012) meta-analytic technique using a voxel-based approach. SDM uses whole-brain co-ordinates or SPM t-maps to calculate effect sizes from each included study, weighted by sample size to account for variance between studies. It has strict criteria for data inclusion such as excluding studies which do not report whole brain results to reduce publication bias. The SDM software package is available for free online (www.sdmproject.com). Analysis was conducted with SDM v5.15. The analysis was thresholded at $p < .005$ and clusters with voxels < 10 were discarded to reduce risk of false positives, in line

with other SDM based reviews (Radua & Mataix-Cols, 2012). Five studies were included (2 using whole-brain co-ordinates, 3 using an SPM t-maps). Data sets that did not provide t-statistics were converted using the SDM package.

4.4 Results

4.4.1 Literature search

The search criteria identified 1,910 goal-conflict (Scopus, n = 1733; PsychInfo, n = 51; Web of Science, n = 25, unique) and 1,348 simple avoidance (Scopus, n = 1083; PsychInfo, n = 115; Web of Science, n = 150, unique) articles. One further article was identified through reference lists. Full text review was conducted on 12 simple-avoidance and 11 goal-conflict studies; four simple-avoidance studies were excluded during full text review due to the paradigm involving passive avoidance only (i.e. participants could not actively respond of their own will to promote/prevent avoidance), in line with our exclusion criteria. After full text review, 11 goal-conflict and eight simple-avoidance experimental papers were included in the systematic review section of this analysis. See Figure 5 for flowchart of selection process.

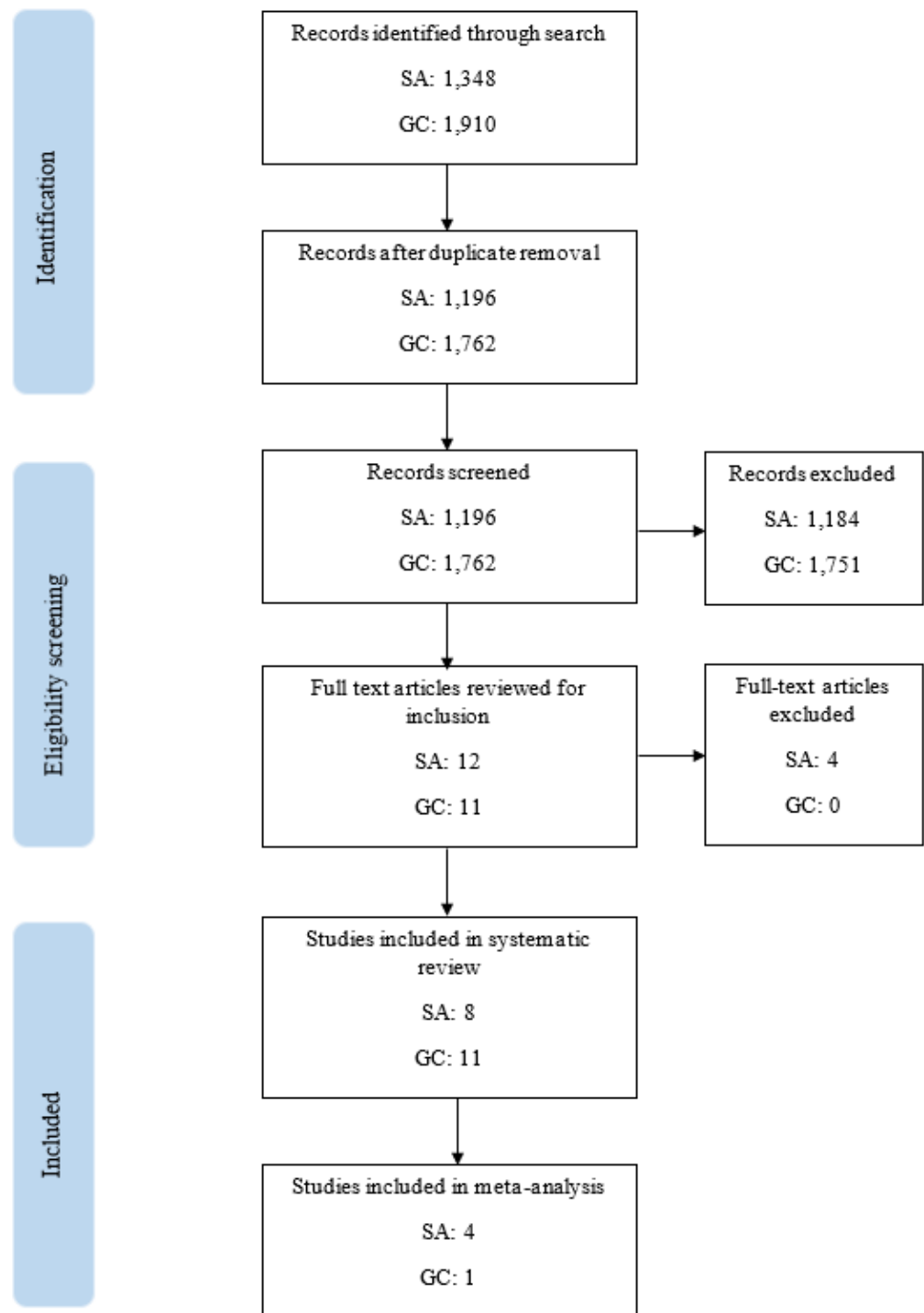


Figure 5 PRISMA diagram of included studies. SA, Simple Avoidance; GC, Goal-Conflict

4.4.2 *Description of selected studies*

The identified paradigms were highly diverse. Simple avoidance tasks included: (1) maze/pathway tasks with virtual predators, $n = 3$; (2) non-chase response to prevent aversive event, $n = 5$. See Table 6 for overview of studies. Goal-conflict were categorized as: (1) maze/open space/runway tasks with virtual predator, $n = 5$; (2) response (option selection) to prevent/encourage event tasks, $n = 6$. See Table 7 for overview of studies. All studies used healthy controls only, and three included pharmacology.

Threat stimuli. Simple avoidance used two types of threat stimuli, physical threat (electric shock, $n = 5$, loud noise, $n = 2$) and loss of tokens/prizes ($n = 1$). Goal-conflict trials tended towards token/prize loss ($n = 6$), but also used physical threat ($n = 2$) and aversive images ($n = 4$).

Goal-conflict rewarding stimuli. Token/prize gain was the most frequent rewarding stimulus ($n = 8$), though pleasant images were also used ($n = 3$).

Table 6

Simple avoidance paradigms

<u>Study</u>	<u>N (male)</u>	<u>Stimuli (threat)</u>	<u>Brief task description</u>
Avoidance of an active predator threat through navigation of avatar			
Mobbs et al. (2007)	14*	Electric shock	Maze navigation to escape virtual predator, stratified as high (3 shocks), low (1 shock) or neutral (0 shocks) threat in active condition. Predator mimicked participant avatar movement only for control trials.
Mobbs et al. (2009)	24 (12)	Electric shock	As in Mobbs et al., 2009 with two additions: visual cues of probability of capture set at 87.5% (high probability) or 12.5% (low probability) and a maze exploration incentive added (participants instructed collect yellow triangles scattered throughout maze).
Collins et al. (2014)	28 (14)	Electric shock	Participants must make navigational movements (specifically, crossing a particular part of the on-screen grid) to avoid aversive outcome when threat symbol is displayed. Incorrect movements would result in aversive event. Participants were not explicitly told the correct navigational movements but learned through trial-and-error. Motor control trials were included in which threat was absent.
Rigoli et al. (2016)	22 (11)	Loud aversive noise burst	Navigation of avatar along a pathway (towards the right) to escape predator appearing far left. Probability of capture set at 50% of trials. Trials either had a visible or an invisible predator (the latter requiring participants to escape without knowledge of predator proximity/speed).
Boeke et al. (2017)	56 (0)	Electric shock	The relationship between face stimuli and shock was taught through fear conditioning in an acquisition phase; faces were presented in pairs, so it was not clear which was the threat. Following this, the faces were again presented but participants could attempt to avoid the aversive outcome associated with them by moving a circle around a grid onscreen, though they were not told which movements would prevent outcome. Participants were either ‘masters’ (made autonomous movements) or ‘yoked’ (passively viewed the movements of their paired master, receiving whatever outcome they received).

<u>Study</u>	<u>N (male)</u>	<u>Stimuli (threat)</u>	<u>Brief task description</u>
Avoidance of threat is achieved through option selection			
Montoya et al. (2015) ⁱ	18 (18)	Aversive image/unpleasant noise	Button press to avoid a threat image (sound pictogram), which rapidly grows to full-size to indicate threat approach. Threats are manipulated to be escapable, imminent (chance-level of escape) or inescapable. Aversive noise was presented as ‘predator attack’ and occurred in the escapable and imminent conditions if the button was not pressed in time. Inescapable trials presented aversive noise and full-size image immediately. Control condition involved the sound pictogram image with a cross through it.
Schlund et al. (2016)	30 (16)	Loss of money	Choice of two options to avoid threat, selection of incorrect option resulted in aversive outcome. Threat stratified as avoidable, unavoidable or safe (control). Participants were not explicitly told the correct choice but learned through practice session trial-and-error.
Wendt et al. (2017)	24 (12)	Electric shock	Experiment had active (threat avoidable with fast button press) and passive (not avoidable, event occurs 50% of the time) trials. The stimuli signalling active vs. passive would grow in size after the participant made their response, indicating how close the threat was getting, culminating in aversive event (if active trial but did not press, or a passive trial with threat) or no event (active trial and pressed, or passive trial with no threat).
* Mobbs et al (2007) did not report the gender of participants			
ⁱ Study administered cortisol or placebo to participants.			

Table 7

Goal-conflict paradigms

<u>Study</u>	<u>N</u> <u>(male)</u>	<u>Stimuli</u> <u>(threat/reward)</u>	<u>Brief task description</u>
Approach and avoidance through navigation of an avatar.			
Bach et al, 2014	19 (19)	Token loss/gain	Participants collect tokens scattered around a virtual space using an avatar, whilst under threat of a predator waking up and chasing them, resulting in the loss of collected tokens. Threat level (risk of predator waking up) were stratified at 20%, 50% or 80% (these probabilities were visually signalled but not explicitly told to participants; one version of the experiment reported instead varied predator speed). Safe spaces were available, where participants could avoid the predator entirely (but not gather tokens); starting position and trial duration were varied randomly.
Aupperle et al, 2015	15 (8)	Aversive images/token gain	Navigation along a runway to indicate choice between two pictures representing outcomes (one at each end). Each outcome was an image-sound pairing - either positive (e.g. a sunshine) or negative (e.g. a cloud) image - combined with a certain level of tokens (0, 2, 4 or 6). If the participant moved to the middle of the runway, they had a 50% likelihood of each outcome; if at either extremity they had a 90% chance of nearest outcome (and 10% of furthest) etc. (so there was never certainty). Conflict trials offered 2, 4 or 6 points for approaching the negative stimuli pairing. Control trials involved simple avoidance (no points, just avoid negative stimuli pairing) and simple approach (few points offered, positive stimuli pairings at both ends).
Gonen et al, 2015	46 (24)	Token loss/gain	Participants earned tokens by catching coins and avoiding balls that interspersed them. Trials were either controlled (where participant actively approach/avoided coins/balls) or uncontrolled (where the participant was hit at random by coins and balls). Game difficulty was modified dynamically as the trials progressed. Trials were also separated in to high and low goal-conflict versions, by manipulating the number of balls the participant must avoid so they can receive the coins. The authors designed a slight bias towards controlled reward to ensure motivation was maintained.

<u>Study</u>	<u>N</u>	<u>Stimuli</u>	<u>Brief task description</u>
	(male)	(threat/reward)	
Approach and avoidance through navigation of an avatar.			
Khemka et al, 2017 ⁱ	25 (11)	Token loss/gain	As in Bach et al, 2017.
Approach and avoidance through option selection			
Talmi et al, 2009	18 (6)	Electric shock/token gain	Participants were presented with a face pairing and a monetary amount. One of the faces was associated with a 75% probability of receiving an outcome (and 25% of getting nothing), and the other with 25% chance (and 75% of getting nothing). Whichever outcome resulted, participants would simultaneously receive an either electric shock or a ‘touch’ (a non-painful shock). A positive token amount, then, would cause conflict between token gain and electric shock avoidance. Participants started with £20 and selected which of the two faces they wanted to ‘play’ with.
Cunningham et al, 2011	18 (8)	Aversive/pleasant images	Participants were presented with a series positive, negative and neutral images (Lang, 2005), one at a time. Participants pressed one button to ‘approach’ and another to ‘avoid’ each image. Avoiding would cause the image to shrink and approaching would cause it to grow to fill the screen. Participants were told to make only one type of response in each block (i.e. approaching all images in the block, regardless of emotional valance) and then switch to a different response for the next block. This was intended to ensure equal approach and avoidance behaviour (and would also cause conflict, as negative images must be ‘approached’).

<u>Study</u>	<u>N</u> <u>(male)</u>	<u>Stimuli</u> <u>(threat/reward)</u>	<u>Brief task description</u>
Approach and avoidance through option selection			
O’Neil et al, 2015	18 (9)	Token loss/gain [†]	In the learning phase, facial and scenery images were presented as pairs to participants and associated as a pair with either reward or punishment (token loss/gain). Participants then saw the pairs recombined as either no-conflict positive (both originally in reward pairs), no-conflict negative (both originally punishment) or conflict (one reward image, one punishment). They had to decide whether to approach or avoid using a button press. No feedback was provided as to the outcome of their decision.
Loh et al, 2016 ⁱⁱ	20 (9)	Token loss/gain	Participants were shown an onscreen grid, hiding both rewards (tokens) and threats (‘bombs’). Participants could not see which were tokens, and were offered a series of choices: they could accept the grid at risk of threat potentially uncovering a reward, they could choose to ‘explore’ (as the cost of a number of tokens) and reveal what is under a portion of the grid (but not the whole grid, meaning threats may still be present) before deciding to take the risk, or they could decline the risk (thus avoiding threat, but also reward). If they accept a grid with only reward, they received tokens, but if they accepted a grid with hidden threats they would lose tokens.
Schlund et al, 2015	30 (16)	Token loss/gain	An initial acquisition phase required participants to pair increasing levels on a vertical bar with increasing probability of the stimuli occurring (probability of loss). In the main task, a reward and a threat level were presented to the participant, and they were given a choice between approaching (causing either gain or loss) or avoiding (avoiding loss, but also preventing gain) by pressing different buttons to indicate their selection.
Radke et al, 2015*	54 (0)	Aversive/pleasant images	Participants were required to use a joystick to ‘approach’ (pulling towards themselves) or ‘avoid’ (pushing away from themselves) emotional face images presented on screen. Participants were told at the start of each block which movement they should make (approaching or avoiding); image size did not change dependent on response, unlike in other uses of this method.
Radke et al, 2017**	57 (57)	Aversive/pleasant images	As in Radke et al, 2015.

* Study administered testosterone or placebo to participants ** Study administered oxytocin or placebo to participants.

ⁱ Magnetoencephalography study ⁱⁱ Analysis did not use conventional MNI space

[†] Token loss/gain only in learning phase, not in decision making phase (only latter took place in fMRI scanner)

4.4.3 *Simple avoidance tasks*

Table 6 details the design of included studies. Defensive distance (i.e. distance from threat), threat anticipation (activation during threat cueing), reception of aversive outcome, and the level of threat presented were varyingly controlled. The latter was manipulated through predetermined probability of capture (e.g. Montoya, van Honk, Bos, & Terburg, 2015; Schlund et al., 2016; Wendt, Löw, Weymar, Lotze, & Hamm, 2017) stratified predator strength (Mobbs, Petrovic, Marchant, Hassabis, & Weiskopf, 2007; Mobbs, Petrovic, et al., 2009) or in one case, visibility of predator (Rigoli, Ewbank, Dalgleish, & Calder, 2016). Trials using spatial navigation and an unpredictability of predator-threat are similar to rodent models, such as the Mouse Defence Test Battery (Blanchard, Griebel, & Blanchard, 2003). Fear conditioning was used in a number of studies, requiring implicit learning of behaviour allowing threat avoidance (Boeke, Moscarello, LeDoux, Phelps, & Hartley, 2017; Collins, Mendelsohn, Cain, & Schiller, 2014; Schlund et al., 2016). Interestingly, only one trial permitted ‘freezing’ behaviour (Wendt et al., 2017). One trial had a pharmacological approach, exploring the role of cortisol in defensive behaviour (Montoya et al., 2015).

4.4.4 *Simple avoidance: neural activation.*

Table 8 shows neural activations in simple avoidance tasks. The key finding was a change from forebrain-to-midbrain activation as the threat came closer; specifically, activation changes from prefrontal cortices to the periaqueductal grey (PAG) and midbrain (Mobbs et al., 2007; Mobbs, Petrovic, et al., 2009; Montoya et al., 2015; Wendt et al., 2017).

Table 8

Neural activation reported in threat avoidance studies

<u>Study</u>	<u>Behaviour/Interaction</u>	<u>Neural activation</u>	<u>Self-report and physiological measures</u>
Avoidance of an active predator threat through navigation of avatar			
Mobbs et al, 2007	Defensive distance	Proximal threat: increased PAG, right dorsal amygdala (CeA, BNST; high threat trials only), dorsal anterior CC, premotor, pons	Post-scan (high) dread was associated with enhanced PAG activity (peaking in DRN) in high and low threat.
		Distal threat: increased ventromedial PFC, subgenual anterior CC, right lateral amygdala (BLA; low threat trials only), medial OFC, lateral PFC, dorsal striatum*	Post-scan low confidence in escape correlated with PAG, and high confidence with ventromedial PFC.
	Threat level	High: Increased PAG, dorsolateral PFC*, hippocampus, CeA	No correlation between these measures observed
		Low: Increased ventromedial PFC, dorsomedial PFC*, dorsolateral PFC*, BLA, fusiform gyrus	
	Threat presence	Increased cerebellum*, PAG* & posterior thalamus*; decreased medial PFC*, right ventromedial PFC* & amygdala*	
	Anticipation of threat	Increased right anterior CC, right medial OFC, ventromedial PFC, Premotor*	

<u>Study</u>	<u>Behaviour/interaction</u>	<u>Neural activation</u>	<u>Self-report and physiological measures</u>
Avoidance of an active predator threat through navigation of avatar			
Mobbs et al, 2009	Defensive distance	Proximal threat: increased midbrain*, mediodorsal thalamus, right striatum, right insula*, dorsal anterior CC*, parietal cortex*, cerebellum*, dorsolateral PFC	SCR was shown to increase from post-encounter to circa-strike, largest for high threat.
		Distal threat: increased posterior CC, bilateral hippocampus, hypothalamus, amygdala, ventromedial PFC, subgenual anterior CC	Anxiety measured pre-encounter, post-encounter and immediately before attack (circa-strike): threat condition was associated with higher anxiety (highest for high threat)
	Threat level	High threat: increased ventromedial PFC (pregenual anterior CC*), dorsomedial PFC, parietal lobule, parahippocampal gyrus	Trait anxiety (STAI) was associated with increased bilateral amygdala and anterior CC activation in high > low threat circa-strike
	Errors under threat	Low threat: no significant voxels Heightened errors correlated with left PAG, dorsal anterior CC, right insula, right midbrain Decreased errors correlated with ventromedial PFC, pregenual anterior CC, temporal pole	
Collins et al, 2014	Threat level	Threat > non-threat: increased bilateral anterior insula*, right dorsolateral PFC*, right caudate*, right PMC* Non-threat > threat: increased left medial PFC*, bilateral posterior insula*, left posterior CC*, left inferior parietal lobule*, left dorsomedial PFC*, left parahippocampal gyrus*, left SMA*, right amygdala*	Anxiety VAS, STAI, COPE, BIS and IMT pre-scan; no correlations between any measure and number of aversive stimuli executed. Anxiety VAS was significantly higher during task (vs. pre- and post- task)

Study	Behaviour/interaction	Neural activation	Self-report and physiological measures
	Threat-avoidance ability	Correlation between avoidance performance and: right amygdala – medial PFC connectivity, amygdala - post-central gyrus connectivity	
Avoidance of threat through option selection			
Montoya et al, 2015	Anticipation	Threat: increased anterior insula*, midbrain*, dorsal anterior CC, supplementary motor area*, left putamen* Non-threat: increased medial TC*, medial OFC*	Fear of threat VAS and POMS recorded pre- and post- cortisol administration to assess parity of groups (no significant difference)
	Threat presence	Threat > non-threat, escapable: no significant voxels; inescapable: anterior insula*, supplementary motor area*, right midbrain, dorsal anterior CC, medial PFC, decreased PFC, medial TC.	Speed of escape as a measure of threat sensitivity, higher in threat relative to safe conditions
	Defensive distance	Threat > non-threat, imminence: anterior insula, midbrain	
Wendt et al, 2017	Defensive distance & threat level	Proximal (high > low threat) increased bilateral anterior insula, ventrolateral PAG, dorsolateral PAG; decreased bilateral amygdala, ventromedial PFC Distal (low > high threat): increased anterior insula, dorsolateral PAG, ventromedial PFC	Heart rate, electrodermal activity and startle blink reflex assessed during training; electrodermal activity higher in anticipation of threat, increasing linearly with threat imminence. Startle potentiation was associated with threat relative to safe conditions
	Receiving stimuli	aversive Increased anterior, middle & posterior insula, anterior & middle cingulate gyrus	

Study	Behaviour/interaction	Neural activation	Self-report and physiological measures
Avoidance of threat through option selection			
Rigoli et al, 2016	Threat visibility	<p>Hidden threat: increased bilateral hippocampus, bilateral amygdala, ventromedial PFC, posterior cingulate*, cuneus*, lingual gyrus*</p> <p>Visible threat: increased PAG, left inferior temporal gyrus*, precuneus*, medial frontal gyrus*, fusiform gyrus*, inferior frontal gyrus*, left cerebellum*</p>	<p>Non-significant correlation between trait anxiety (STAI) and probability of escape VAS rating.</p> <p>Positive association between STAI score and left hippocampal activation in hidden threat condition; positive association between probability of escape VAS and left hippocampal at trial start, but not end</p>
Schlund et al, 2016	Threat level	<p>Unavoidable threat > non-threat: increased dorsal anterior CC, dorsomedial PFC</p> <p>Unavoidable threat > avoidable: increased left dorsomedial PFC, left pregenual anterior CC, right ventromedial PFC</p>	<p>Threat ratings higher after threat conditioning; ratings for avoidable threat were significantly lower than for unavoidable threat, but safe condition significantly lower than both</p>
Boeke et al, 2017	Threat level	Threat vs. no threat: increased putamen, caudate, medial PFC [†]	<p>SCR was not shown to correlate with behaviour or with feelings of control during task.</p> <p>STAI, IUS and PSS measured prior to task, to assess parity between groups</p>
PAG, periaqueductal grey; CeA, central amygdala; BNST, basal nuclei of stria terminalis; CC, cingulate cortex; PFC, prefrontal cortex; BLA, basolateral amygdala; OFC, orbitofrontal cortex; DRN, dorsal raphe nucleus; SCR, Skin Conductance Response; STAI, State-Trait Anxiety Inventory; TC, temporal cortex; VAS, Visual Analogue Scale; POMS, Profile of Mood States questionnaire; SMA, supplementary motor area; BIS, Barrat's Impulsivity Scale; IMI, Intrinsic Motivation Inventory; IUS, Intolerance of Uncertainty; PSS, Perceived Social Stress scale.			

*Significant at $<.05$ corrected for multiple comparisons (i.e. surviving whole-brain analysis correction)

† Paradigm compared master (active) and yoked (passive) participants, interactions reported are master > yoked; yoked > masters revealed ventromedial PFC activation increase (ROI analysis only).

4.4.4.1 Prefrontal areas

Increased activity in prefrontal areas (ventromedial, dorsolateral and dorsomedial PFC) and cingulate cortices (CC; anterior and/or posterior) was observed in response to threat presence generally (Collins et al., 2014; Mobbs, Petrovic, et al., 2009; Montoya et al., 2015; Schlund et al., 2016). Specifically, activation in these areas was associated with distal (Mobbs et al., 2009; Mobbs et al., 2007; Wendt et al., 2017), unavoidable (relative to avoidable) (Montoya et al., 2015; Schlund et al., 2016), or hidden (relative to visible) (Rigoli, Pavone, & Pezzulo, 2012) threat. Heightened activity in these areas were commonly associated with high threat levels (Boeke et al., 2017; Collins et al., 2014; Mobbs et al., 2007; Mobbs, Petrovic, et al., 2009; Montoya et al., 2015; Wendt et al., 2017), though occasionally dorsal medial PFC area activation was present in low/absent threat situations (Collins et al., 2014; Mobbs et al., 2007). However, a handful of these paradigms also highlighted the anterior CC in proximal threat (Mobbs et al., 2007; Mobbs, Petrovic, et al., 2009). Ventromedial PFC activation was shown to correlate with decreased locomotor errors during escape from threat, in one study (Mobbs, Petrovic, et al., 2009).

4.4.4.2 PAG & midbrain

PAG and midbrain areas were shown to activate in response to threat presence (Boeke et al., 2017; Collins et al., 2014). In contrast to the PFC, heightened activation in the PAG and midbrain areas was observed when threat was proximal and/or high (Mobbs et al., 2007; Mobbs, Petrovic, et al., 2009; Wendt et al., 2017), or visible (relative to invisible; Rigoli et al., 2012). Complementing prefrontal data, PAG and midbrain activation were linked to increased locomotive errors (Mobbs, Petrovic, et al., 2009); though somewhat contradictorily the anterior CC was also engaged. One trial suggested that midbrain activation in response to threat may be modulated by cortisol levels (Montoya et al., 2015).

4.4.4.3 Insula cortex

Anterior insula activation was associated with presence of threat (Collins et al., 2014; Montoya et al., 2015), with some evidence of differential posterior activation in threat-absent trials (Collins et al., 2014). This dual purpose was also present in regards to defensive distance, with both proximal (Mobbs,

Petrovic, et al., 2009; Wendt et al., 2017) and distal (Wendt et al., 2017) threats leading to heightened BOLD response. Anterior insula activation was linked to increased errors during threat exposure (Mobbs, Petrovic, et al., 2009), anticipation of threat (Montoya et al., 2015) and reception of aversive stimuli due to non-avoidance of threat (Wendt et al., 2017).

4.4.4.4 Limbic system

Unsurprisingly, the amygdala was shown to respond to presence of threat, whether proximal (Mobbs et al., 2007; Mobbs, Petrovic, et al., 2009; Wendt et al., 2017), distal (Mobbs, Petrovic, et al., 2009) or hidden (Rigoli et al., 2012). Dorsal amygdala function was specifically linked to threat proximity, whilst basolateral amygdala (BLA) function was associated with distal threat (Mobbs et al., 2007), though other studies have found the direction of this finding to be variable (Montoya et al., 2015; Wendt et al., 2017), potentially due to issues in subdividing the amygdala accurately. Thalamus (posterior and mediodorsal) and hypothalamus activation were linked to threat presence, regardless of distance from the subject, though the hippocampal structures activated only in response to distal (Mobbs, Petrovic, et al., 2009) and high (Mobbs et al., 2007) threat levels. The hippocampus also reacted during exposure to hidden threat (Rigoli et al., 2012), and curiously during non-threat exposure in one trial (Collins et al., 2014).

4.4.5 *Goal-conflict tasks*

The types of goal-conflict task were similar to those used in simple avoidance. A subset of the navigation paradigms limited response to a restricted runway, with participants able to show level of approach/avoidance behaviour by placement along it (Aupperle, Melrose, Francisco, Paulus, & Stein, 2015; Schlund, Brewer, Richman, Magee, & Dymond, 2015). In tasks requiring option selection to indicate response, 3 paradigms used pressure-sensitive joysticks to indicate choice (Cunningham et al., 2011; Radke et al., 2017, 2015). Threat (and/or reward) level was manipulated as in simple avoidance. This was via stratified threat/reward pairings (Loh et al., 2016; Schlund et al., 2015), probability of threat/reward (Bach et al., 2014; Khemka, Barnes, Dolan, & Bach, 2017; Talmi, Dayan, Kiebel, Frith, & Dolan, 2009) or both (Aupperle et al., 2015; Gonen et al., 2016). A number of studies removed

choice, telling participants which action to use (Cunningham et al., 2011; Radke et al., 2017, 2015). One paradigm removed in-trial feedback entirely, presenting only stimuli conditioned as threat or reward representations (O’Neil et al., 2015). Pharmacological intervention featured in two paradigms by the same authors, one exploring testosterone (Radke et al., 2015) and the other oxytocin (Radke et al., 2017). A full outline of the paradigms included is shown in Table 7.

4.4.6 Goal-conflict, neural activation

Neural activations are displayed in Table 9. Paradigms compared conflict and non-conflict situations, varied threat/reward level and assessed activation associated with motivational direction.

Table 9			
Neural activation in goal-conflict studies			
<u>Study</u>	<u>Behaviour/Interaction</u>	<u>Neural activation</u>	<u>Self-report and physiological measures</u>
Approach and avoidance through navigation of an avatar			
Aupperle et al, 2015	Conflict vs. no conflict	<p>Conflict: increased right rostral & dorsal CC, right dorsolateral PFC, bilateral interior insula & bilateral caudate</p> <p>No conflict: increased bilateral posterior insula, dorsal mid-cingulate, left lateral PFC</p>	No significant association between trait anxiety (STAI) and task performance
Schlund et al, 2015	Conflict level	<p>Smaller difference in outcome value: increased pregenual & dorsal anterior CC, dorsal & ventral cingulate, anterior insula and inferior frontal regions</p> <p>Larger difference in outcome value: increased ventromedial PFC and dorsolateral PFC</p> <p>At threshold between outcome values: peak activation, OFC and ventral hippocampus</p>	SCR to threat stimuli increased after conditioning (in a separate experiment to neuroimaging, within same publication)
Bach et al, 2014	Threat level	As threat level increased, increased activity in the hippocampus, extending in to posterior amygdala, left parahippocampal gyrus*, left fusiform/parahippocampal gyrus*, right inferior frontal gyrus/insula*	N/A

<u>Study</u>	<u>Behaviour/interaction</u>	<u>Neural activation</u>	<u>Self-report and physiological measures</u>
Approach and avoidance through navigation of an avatar			
Gonen et al, 2015	Conflict level ¹	<p>High conflict: increased left VTA*, bilateral pulvinar*, bilateral precuneus*, bilateral occipital lobe*, bilateral premotor cortex*, bilateral VS*, right middle frontal gyrus*, PAG*</p> <p>Low conflict: increased bilateral superior temporal gyrus*, bilateral ventrolateral PFC*, right superior frontal gyrus*, right IFC*, medial PFC*, posterior CC*</p>	<p>SCR significantly higher in active threat trials.</p> <p>Grouped participants as high approach or high avoidance, depending on NEO-FFI, TPQ and SPSRQ scores; significant difference between groups in VTA and VS activation, with higher activation in approach group during high goal conflict.</p>
Khemka et al, 2017 ²	Threat level	<p>High threat: increased right hippocampal oscillation, decreased left hippocampal oscillation</p> <p>Token appearance (high > low threat): increased bilateral middle frontal gyrus oscillation</p>	N/A
Approach and avoidance through option selection			
Talmi et al, 2009	Sensitivity to pain	High pain: increased activity in somatosensory cortex*	
	Reward prediction ³	Errors: increased activity in ventromedial PFC, OFC, anterior & posterior CC, VS, insula, hippocampus/amygdala, superior frontal/middle frontal gyri, fusiform gyrus, Rolandic operculum	SCRs in response to pain were higher in trials with zero or negative reward, indicating pain attenuated response to reward

<u>Study</u>	<u>Behaviour/interaction</u>	<u>Neural activation</u>	<u>Self-report and physiological measures</u>
Approach and avoidance through navigation of an avatar			
Cunningham et al, 2011	Stimuli valence	Increased right amygdala activity for positive and negative stimuli, relative to neutral	Grouped participants by BFAS score in to Neuroticism-withdrawal or Neuroticism-volatile; former predicted amygdala response to approached stimuli, latter associated with amygdala response to negative stimuli
	Motivational direction	Approach > avoid: increased amygdala activity	
			Measured BIS/BAS self-report, but no associations observed
O'Neil et al, 2015	Conflict vs. no conflict	Conflict: increased bilateral posterior hippocampus*, posterior cingulate gyrus*, paracingulate gyrus*, frontal pole*, OFC*, anterior CC*, amygdala*, putamen*, caudate*	N/A
	Motivational direction	Approach: increased anterior hippocampus*, parahippocampal cortex*, paracingulate gyrus*, temporal fusiform cortex*, OFC, insular cortex*, thalamus*, frontal pole*, inferior temporal gyrus* & entorhinal cortex*	
Radke et al, 2015	Conflict vs. no conflict	Conflict: increased anterior PFC activity (testosterone & placebo)	Recorded NEO-FFI, BIS/BAS, STAI, IRI and PRF means, but no interactions explored
	Motivational direction	Testosterone in approach: increased right amygdala activity Testosterone in avoid: decreased amygdala activity	

<u>Study</u>	<u>Behaviour/interaction</u>	<u>Neural activation</u>	<u>Self-report and physiological measures</u>
Approach and avoidance through navigation of an avatar			
Radke et al, 2017	Conflict vs. no conflict	Conflict: increased anterior PFC* activity, left middle temporal gyrus*, left medial FC*, left inferior parietal lobule*, left paracentral lobule*, bilateral postcentral gyrus*, right superior temporal gyrus* (all oxytocin & placebo)	LAS measure of anxiety recorded post-scan, but no significant associations shown
	Motivational direction	Approach: decreased right amygdala (oxytocin); no effect in avoidance	
Loh et al, 2017	Decision making	Avoidance of loss: bilateral inferior hippocampus activation Choice phase: increased bilateral dorsolateral PFC*, parietal cortex*, cerebellum*, right striatum*, occipital cortex*, insula*, bilateral hippocampus* Exploration phase: increased right striatum*, rostromedial frontopolar cortex*, middle frontal gyrus *, superior frontal gyrus* & parietal cortex*	Trait anxiety (STAI) shown to correlate with behaviour in response to conflict (i.e. likelihood of choosing to avoid threat in approach-avoidance and of accepting offer in approach-avoidance)

VTA, ventral tegmental area; VS, ventral striatum; CC, cingulate cortex; PFC, prefrontal cortex; OFC, orbitofrontal cortex;; PAG, periaqueductal grey; IFC, inferior frontal cortex;; STAI, State-Trait Anxiety Inventory; SCR, Skin Conductance Response; NEO-FFI, NEO Five Factor Inventory; TPQ, Tri-dimensional Personality Questionnaire; SPSRQ, Sensitivity to Punishment and Reward Questionnaire; BFAS, Big Five Aspect Scale; BIS/BAS, Behavioural Inhibition System/Behavioural Activation System Scales; IRI, Interpersonal Reactivity Index; PRF, Personality Research Form.

¹ Only approach behaviour in controlled trials analysed due to lack of avoidance behaviours ²Magentoencephalography (MEG) study ³Analysis restricted to areas activated by main effect of pain (whole-brain) across the whole group

4.4.6.1 Prefrontal areas

Prefrontal and CC activation was associated with conflict (Aupperle et al., 2015; Radke et al., 2017, 2015), though not necessarily high conflict (Gonen et al., 2016). PFC activation was also associated with errors during reward prediction (Talmi et al., 2009) and activated during decision-making generally (Loh et al., 2016), suggesting an assessment role for these areas. A point of separation is observed in PFC activation during large value-outcome (reward vs threat) differences, and CC activation in response to small value-outcome differences (Schlund et al., 2015).

4.4.6.2 PAG and midbrain regions

Relative to threat avoidance, the PAG and midbrain regions featured less here. PAG activation was activated in high conflict (Gonen et al., 2016), as were the putamen, caudate and thalamus (Aupperle et al., 2015; O'Neil et al., 2015).

4.4.6.3 Insula cortex

Insula activity was widely relevant, indicated in response to conflict (Aupperle et al., 2015), increasing threat (Bach et al., 2014), errors in reward prediction (Talmi et al., 2009), choice selection (Loh et al., 2016), approach (relative to avoidance) (O'Neil et al., 2015) and small value-outcome differences (Schlund et al., 2015). Conversely, this area also activated in response to non-conflict scenarios (Aupperle et al., 2015).

4.4.6.4 Limbic system

Activation of the hippocampus (and parahippocampal gyri) was associated with conflict (O'Neil et al., 2015), decision making (Loh et al., 2016), increased threat (Bach et al., 2014), approach (O'Neil et al., 2015) and successful avoidance of loss (Loh et al., 2016). One study used a ROI MEG approach, identifying increased hippocampal oscillation in the right, and decreased in the left, hemisphere during high threat conflict (Khemka et al., 2017). Hippocampal activation was also associated with threshold of outcome-values, when the value-difference between outcomes is smallest (Schlund et al., 2015). As in simple avoidance, amygdala activation was raised in high threat scenarios (Bach et al., 2014), as well

as during conflict (O'Neil et al., 2015). Stimuli and motivational valence was also linked to the amygdala, with increased activity in response to emotional stimuli (Cunningham et al., 2011) and approach behaviour (Cunningham et al., 2011; Radke et al., 2017), the latter reflective of activation during proximal threat outlined in simple avoidance (Mobbs et al., 2007; Mobbs, Petrovic, et al., 2009). One trial indicated testosterone in amygdala response, increasing activation during approach and decreasing during avoidance (Radke et al., 2015). Similarly, oxytocin may play a role, as indicated by amygdala deactivation during approach, though not avoidance (Radke et al., 2017). Figure 6 gives a visual representation of the key findings of the systematic review.

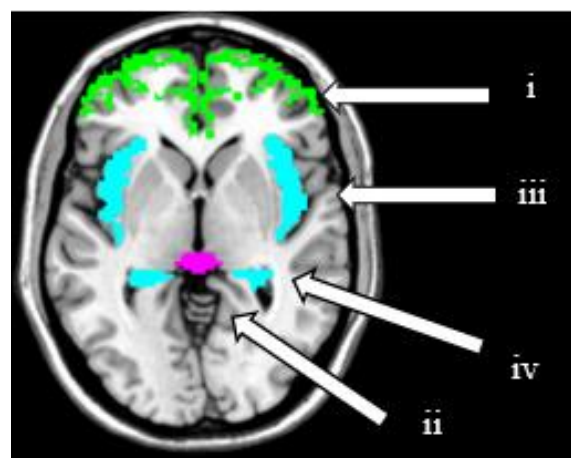


Figure 6 Regions reported in systematic review of human defensive behaviour: i) ventromedial and dorsolateral prefrontal cortices showing higher activation in response to distal threats; ii) midbrain and periaqueductal grey regions showing higher activation in response to proximal threats; iii) insular cortices, activating in response to conflict and threat; iv) hippocampus and amygdala (posterior hippocampus shown), the amygdala activates in response to threat, and hippocampus, showing activation in simple avoidance and goal-conflict trial types, though when motion is controlled for hippocampal activation appears relevant to goal-conflict trials only. Figure made in MRICron using SPM masks.

4.4.7 Self-report and physiological data for paradigm validation

Not all paradigms used self-report or physiological data as validation of threat/reward experience. Skin conductance response (SCR) (Gonen et al., 2016; Mobbs, Petrovic, et al., 2009; Schlund et al., 2016; Talmi et al., 2009; Wendt et al., 2017) or self-report anxiety (Collins et al., 2014; Loh et al., 2017; Mobbs, Petrovic, et al., 2009) were used to support threat value, though not always successfully (Aupperle et al., 2015; Boeke et al., 2017; Radke et al., 2017; Rigoli et al., 2016). Brain activity was

also validated with self-report, as shown in the association between PAG activation and self-reported feelings of dread (Mobbs et al., 2007).

4.4.8 Individual differences

Few studies explored personality or trait characteristics in the context of defensive behaviour. Despite predictions around neuroticism as the core of defensive behaviour (McNaughton & Corr, 2004), the State-Trait Anxiety Inventory (STAI) (Spielberger, Gorsuch, & Lushene, 1970) was the mostly commonly used measure of individual differences. Heightened amygdala and anterior CC response to high threat was linked to trait anxiety (Mobbs, Petrovic, et al., 2009). Trait anxiety was also correlated with behavioural response to conflict (i.e. choosing to avoid, rather than approach) (Loh et al., 2017) and left hippocampal activation during exposure to hidden threat (Rigoli et al., 2016). Amygdala response to conflict was also predicted by neuroticism in one trial (Cunningham et al., 2011): individuals were grouped as ‘neurotic-withdrawn’ or ‘neurotic-volatile’ with the former predicting amygdala response to approach, and the latter amygdala response to negative stimuli. Individual differences in personality were also shown to have an impact on threat sensitivity, as represented individuals with greater approach tendencies, dictated by scores on the NEO-Five Factor Inventory (Costa & McCrae, 1992), Tri-dimensional personality questionnaire (Cloninger, 1987) and sensitivity to punishment and reward questionnaire (Torrubia, Avila, Molto, & Caseras, 2001), having greater VTA and VS activation in high conflict scenarios (Gonen et al., 2016). See Table 8 and Table 9 for further details.

4.4.9 Meta-analysis of simple avoidance open space/maze tasks

As heterogeneity between tasks was high, five studies with comparable designs were included in a meta-analysis of avoidance of threat (n = 151 healthy control participants across the 5 independent publications). These studies were included based on similarity of contrasts analysed (i.e. all studies included analysis comparing avoidance in high vs. low or absent- threat conditions). Of the 8 simple-avoidance studies included in the systematic review, 4 were not included in the meta-analysis (due to fundamental difference in contrasts, e.g. not directly comparing high vs. low/absent threat, n = 2; and

due to availability of data, i.e. no whole-brain co-ordinates or t-maps available, $n = 2$). One goal-conflict study (Bach et al., 2014) included a simple-avoidance contrast analysed separately from the goal-conflict analysis, and so this contrast was also included in the simple-avoidance meta-analysis. A meta-analysis of neural activation in goal-conflict was not possible, due to study design and contrast analysis heterogeneity. Studies using Montreal Neurological Institute (MNI), Talarach and FMRIB Software Library (FSL) standardised space and providing either whole-brain co-ordinates or SPM statistical maps were included. See Table 10 for details of studies and contrasts.

Table 10

Details of studies included in pooled-data analysis

<u>Study</u>	<u>N</u>	<u>Contrasts</u>	<u>Thresholding</u>	<u>Data type</u>
Mobbs et al, 2009	24	Escape from predator, high vs. low threat*	<.001 uncorrected	Whole-brain coordinates
Bach et al, 2014 [†]	19	Escape from predator, high vs. low threat*	<.05 corrected	SPM t-map
Collins et al, 2014	28	Escape from threat, threat vs. non-threat*	<.05 corrected	Whole-brain coordinates
Wendt et al, 2017	24	Avoiding threat, threat vs. non-threat**	<.001 corrected	SPM t-map
Boeke et al, 2017 ^{††}	56	Avoiding threat, threat vs. non-threat**	<.05 corrected	SPM t-map

SDM, Seed-based d Mapping; SPM, Statistical Parametric Mapping

[†] Goal-conflict paradigm, but simple avoidance available for SDM analysis

^{††} Study used FSL stereotactical space

* Movement of on-screen avatar to escape threat

** Button press to signal decision to avoid threat

As shown in Table 11 several common brain regions were identified, mostly centred on the frontal gyri. Jack-knife sensitivity analysis was conducted to assess robustness; no finding was reliably present across all five studies.

Table 11

Areas of activation and deactivation identified in pooled-data analysis, high threat vs. low- or absent-threat.

<u>Region</u>	<u>Peak MNI coordinate</u>	<u>SDM value</u>	<u>Z-</u>	<u>P</u>	<u>Voxels</u>	<u>BA</u>	<u>Heterogeneity⁷</u> <u>(n = 5 studies)</u>
Activations							
R superior frontal gyrus, medial ¹	4, 38, 38	9.094		<.001	2664	9	0
R superior frontal gyrus, dorsolateral	22, 42, 38	3.960		<.001	35	9	0
R superior frontal gyrus, dorsolateral	20, 56, 24	3.065		.002	11	10	5.2
R middle frontal gyrus ²	40, 28, 36	4.317		<.001	1735	45	0
R middle frontal gyrus ¹	28, 52, 22	3.564		<.001	141	46	0
L superior longitudinal fasciculus III	-38, 16, 10	4.063		<.001	705	-	0
R superior longitudinal fasciculus III	44, -48, 36	3.276		.001	19		5.8
R supramarginal gyrus ³	56, -44, 32	3.628		<.001	247	48	4.3
Cerebellum, vermic lobule IV/V	0, -64, -6	3.052		.002	29		0
Deactivations							
L superior temporal gyrus ⁴	-60, -12, 10	-3.832		<.001	1184	22	12.6
R fronto-insular tract 5	52, -10, 18	-3.556		<.001	821	-	0
L gyrus rectus	-4, 46, -20	-3.261		<.001	854	11	3.5
L precuneus	-10, -54, 30	-3.259		<.001	626	23	20.9
L middle frontal gyrus ⁵	-22, 26, 44	-3.420		<.001	303	9	0
L superior frontal gyrus, dorsolateral	-14, 62, 16	-2.398		<.001	45	10	0
L inferior frontal gyrus, triangular part	-50, 28, 20	-2.33		<.001	37	45	0
L middle frontal gyrus, orbital part	-22, 36, -16	-2.472		<.001	24	11	0.4

<u>Region</u>	<u>Peak MNI</u> <u>coordinate</u>	<u>SDM</u> <u>value</u>	<u>Z-</u> <u>P</u>	<u>Voxels</u>	<u>BA</u>	<u>Heterogeneity</u> ⁷ <u>(n = 5 studies)</u>
Deactivations						
L middle temporal gyrus	-60, -6, -10	-2.312	<.001	41	22	0.6
L middle temporal gyrus	-52, -32, 8	-2.406	<.001	11	22	0
L inferior temporal gyrus	-56, -48, -12	-2.476	<.001	20	20	62.3
R temporal pole, superior temporal gyrus ⁶	40, 6, -22	-2.712	<.001	31	38	12.2
R cerebellum, crus I	28, -72, -36	-2.347	<.001	25	-	0
R cerebellum, crus II	46, -68, -40	-2.130	.002	16	-	0
R parahippocampal gyrus	16, -6, -26	-2.521	<.001	7	28	0
Olfactory cortex	2, 12, -10	-2.467	<.001	3	25	0

R, Right; L, Left; MNI, Montreal Neurological Institute; SDM, Seed-based d Mapping; BA, Brodmann Area

¹ Driven by 3/5 studies: Boeke et al, 2017, Collins et al, 2014, Bach et al, 2014

² Driven by 4/5 studies: Boeke et al, 2017, Bach et al, 2014, Wendt et al, 2017, Collins et al, 2014

³ Driven by 4/5 studies: Bach et al, 2014, Wendt et al, 2017, Mobbs et al, 2009, Collins et al, 2014

⁴ Driven by 4/5 studies: Bach et al, 2014, Boeke et al, 2017, Mobbs et al, 2009, Collins et al, 2014

⁵ Driven by 4/5 studies: Bach et al, 2014, Boeke et al, 2017, Wendt et al, 2017, Mobbs et al, 2009

⁶ Driven by 4/5 studies: Mobbs et al, 2009, Wendt et al, 2017, Collins et al, 2014

⁷ Heterogeneity scores (0-100) calculated in MRICron.

All areas driven by ≥ 4 studies are indicated in the table as particularly robust. Activation of the right medial prefrontal cortex region (middle frontal gyrus) but deactivation of the left middle frontal gyrus was present in all but 1 study during exposure to threat, as indicated in Table 11. In contrast to the systematic review, midbrain activation during greater threat and forebrain activation in lower threat was not shown in the meta-analysis. Funnel plots were created for all regions driven by ≥ 4 studies. The funnel plots appeared well distributed and all Egger's bias tests were non-significant suggesting minimal bias. However, caution is advised when interpreting plots with small numbers of studies. Too

few studies were available to perform meta-regression to assess heterogeneity (Radua, van den Heuvel, & Surguladze, 2010) between response types (button press vs. avatar movement). Figure 7 (MRICron; www.nitrc.org) shows activations and deactivations relating to threat level prior to jack-knife analysis.

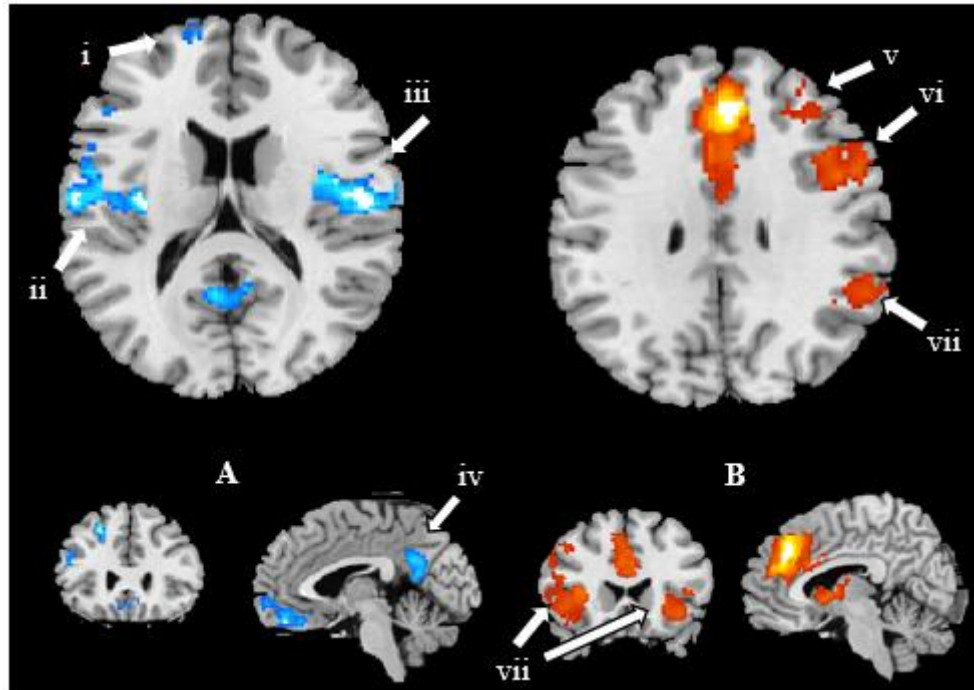


Figure 7 Brain regions identified in avoidance in threat vs. low or non-threat. A) Deactivations in high vs. low threat (SDM threshold regions of > 10 voxels, peak Z value = 3.1); B) Activations in high vs. low threat (SDM threshold regions of > 10 voxels, peak negative Z value = -2.130. Deactivations (in threat vs. low/non-threat) are indicated in the left-side panel (A), with shades of blue reflective of intensity of deactivation in the: i) left superior frontal gyrus (-14, 62, 16); ii) left superior temporal (-60, -12, 10) and middle frontal (-22, 26, 44) gyri; iii) right temporal pole (40, 6, -22) & fronto-insula tract (52, -10, 18); iv) left precuneus (-10, -54, 30). Activations (in threat vs. low/non-threat) are shown in the right-side panel (B): v) right superior frontal gyrus, dorsolateral (22, 42, 38) & medial (4, 38, 38); vi) right middle gyrus (40, 28, 36); vii) right supramarginal gyrus (56, -44, 32); viii) left (-38, 16, 10) & right (44, -48, 36) superior longitudinal fasciculus. Image created in MRICron, using SDM output.

4.5 Discussion

This review explored neural activation in human defensive reactions. Simple avoidance was characterised by a forebrain-to-midbrain change in activation as threat approaches (Mobbs et al., 2007; Mobbs, Petrovic, et al., 2009; Montoya et al., 2015; Wendt et al., 2017), supported in the review via differential midbrain and forebrain activation (Montoya et al., 2015; Rigoli et al., 2012). A cortical-subcortical change is in line with animal work (Blanchard, 2017) and prominent theories of human

defence (Corr, 2013; McNaughton & Corr, 2004). It also reflects the clinical literature, as shown in PFC activation in anxiety (Myers-Schulz & Koenigs, 2012) and PAG association with panic (Canteras & Graeff, 2014) (see figure 1). Observed PFC and PAG functional connectivity (Chan et al., 2011) supports the concept of interactive suppression dependent on threat proximity (Mobbs et al., 2007).

More innate bottom-up processing may lead in situations requiring fast response to imminent threat, with higher-order processing associated with evaluative responses to proximal threat and decision making. In support, conflict and decision-making was linked to high-order areas such as the PFC and CC in goal-conflict trials (Aupperle et al, 2015; Loh et al., 2017) and more accurate escape behaviour (Mobbs, Petrovic, et al., 2009), as well as difficult-to-gauge threat, whilst PAG activation was shown in response to clear threat (Rigoli et al., 2012). Change in activation from the dorsal PFC through posterior cingulate, septo-hippocampal system, the amygdala, the medial hypothalamus to the PAG during increasing defensive approach is also predicted in the literature (McNaughton & Corr, 2004). This review provides some support for this, as threat-approach and exploration was also shown to involve the PAG, midbrain and limbic areas (Bach et al., 2014; Cunningham et al., 2011; O'Neil et al., 2015). The pattern of activation revealed by the systematic review is reminiscent of the default mode network (DMN), with both the CC and PFC key components (Greicius, Krasnow, Reiss, & Menon, 2003). There is evidence to suggest the DMN may be altered in individuals with anxiety disorder (Zhao et al., 2007), supporting the concept of these regions as intrinsic to anxiety-related neural circuitry and behaviour. Further, the DMN has been proposed as integral to neuroticism and self-generated thought processes (Perkins, Arnone, Smallwood, & Mobbs, 2015), including cognitive processes such as worry, which is integral to anxiety disorders (American Psychiatric Association, 2013a).

Conflict was linked to both subcortical (insula, midbrain, PAG, hippocampus and amygdala; Aupperle et al., 2015; Bach et al., 2014; Gonen et al., 2016; Khemka et al., 2017) and cortical (PFC and CC; Gonen et al., 2016) activation. Frontal activation is as expected, considering the role of PFC and CC in conflict monitoring (Botvinick, 2007) and executive functioning (Koechlin & Summerfield, 2007). Interestingly, PFC response to conflict is modulated by testosterone (Radke et al., 2015), with clinical implications for maladaptive approach behaviours; as the tested sample were all male, no comment can

be made on how gender differences may feature in this relationship. Theories hold a tentative role for the (anterior) CC in conflict resolution in defensive behaviour, and (particularly the dorsal aspect of) both the CC and PFC (McNaughton & Corr, 2004), which is supported here. One study stratified conflict, indicating higher conflict was mostly associated with subcortical regions, and lower conflict with cortical (Gonen et al., 2016), reflective of threat proximity findings in simple avoidance. However there is far from a consensus as a number of studies report PFC and/or CC activation during absence of conflict (Aupperle et al., 2015; Gonen et al., 2016) suggesting further work is required.

The insula activation was shown in both simple avoidance and goal-conflict. The insula has previously been associated with conflict (Roberts & Hall, 2008) stimuli salience (Stein & Paulus, 2009), processing of pain and bodily sensation (Kirlic et al., 2017; Talmi et al., 2009), potentially relaying to the amygdala (Phelps et al., 2001). Seeley et al identified a salience-value processing network including the anterior insula, amygdala and dorsal/anterior CC (Seeley et al., 2007). Anterior CC, anterior insula and inferior frontal regions activation was observed when difference between threat and reward outcomes was increased (i.e. both outcomes have high salience), and ventromedial and dorsolateral PFC activation when decreased (Schlund et al., 2015). Frontal-cortical regions and the CC have been shown to activate in low goal-conflict (Gonen et al., 2016), and conflict present vs. absent situations (Aupperle et al., 2015; O'Neil et al., 2015) though this activation was not exaggerated in higher goal-conflict. The VTA and VS showed increased activity in higher conflict (Gonen et al., 2016), in line with animal work suggesting a role for these areas in motivational response (Haber & Knutson, 2010; Williams, Rolls, Leonard, & Stern, 1993). The reward system is pertinent here, considering the role of the OFC, anterior CC, VS and amygdala identified in this review, and within the reward-circuitry of the human brain (Haber & Knutson, 2010). Deactivation of the right fronto-insular tract was noted in the meta-analysis; the insula is typically involved in processing of conflict and bodily sensation/pain (Kirlic et al., 2017; Roberts & Hall, 2008), deactivation of its connections with frontal regions could reflect deactivation of frontal processing in high threat due to reliance on innate bottom-up processing.

The hippocampus is considered integral to approach-avoidance conflict specifically (Ito & Lee, 2016; Perkins et al., 2013), as it is linked to sustained anxiety rather than fear (McNaughton & Corr, 2004).

Anxiety is likely related to more distal and unpredictable fears (Davis et al., 2010), reflective of the hippocampal activity observed here. A key role of the hippocampus is spatial function and memory (Eichenbaum & Cohen, 2014). Hippocampal involvement in simple avoidance was present in tasks involving a high degree of spatial functioning, whether navigation within a ‘maze’ (Mobbs, Petrovic, et al., 2009), prediction of spatial location of an invisible threat (Rigoli et al., 2016), or specific spatial orientation (Collins et al., 2014). Goal-conflict trials involving hippocampal activation did include some spatial processing (Bach et al., 2014; Khemka et al., 2017; Schlund et al., 2015), but unlike simple avoidance hippocampal activation was also observed in goal-conflict tasks without spatial demands (Loh et al., 2016; O’Neil et al., 2015; Talmi et al., 2009). These findings support a distinct role for the hippocampus in goal-conflict beyond spatial processing, in line with prominent theories (McNaughton & Corr, 2004) and animal work (Kirlic et al., 2017).

Amygdala activation was observed in response to threat (Mobbs et al., 2007; Mobbs, Petrovic, et al., 2009), as in animal models (Blanchard, 2017; Davis et al., 2010). Amygdala response in defensive distance is thought to divide across both anticipation and avoidance of threat (see figure 1) (Canteras & Graeff, 2014). Research has distinguished basolateral amygdala (BLA) and the central amygdala (CeA)/basal nucleus of the stria terminalis (BNST) activation, though these regions are highly interconnected (Davis et al., 2010; Dong, Petrovich, & Swanson, 2001). The BLA is associated with threat value judgement via connections with the ventromedial PFC and OFC and the CeA/BNST with behavioural and basic autonomic system activity via the PAG (Fanselow, 1994; Mobbs, Petrovic, et al., 2009; Quirk, Likhtik, Pelletier, & Paré, 2003). Animal work indicates the CeA and the BNST are distinct, contributing to fear and anxiety respectively (Kumar et al., 2013), with improved avoidance behaviour after CeA lesions (LeDoux et al., 2017). Whilst human amygdala lesions are associated with reduced fear behaviour in response to threat (Korn et al., 2016), lesions restricted to the BLA have been linked to fear hypervigilance (Terburg et al., 2012). Though not distinguished in goal-conflict paradigms, one simple avoidance experiment associated the BLA and CeA with low and high threat, respectively (Mobbs, Petrovic, et al., 2009). The BLA in particular has been proposed as a factor in the cortical-to-subcortical activation change in fear responding through its inhibitory role (Terburg et al.,

2012). Activation of regions such as the CeA and BNST are of clinical interest, given evidence that N-methyl-D-aspartate receptor function facilitation can increase context-specific extinction (Perusini & Fanselow, 2015; Walker & Davis, 2002), with clear implications for treatment. Similarly, separation of anterior and posterior cingulate cortical regions has been hypothesised representing defensive avoidance and defensive approach at roughly equivalent distances (McNaughton & Corr, 2004), though this is not supported in this review.

Though the systematic review supports RST and animal work, the meta-analysis did not support these findings. Prefrontal areas accounted for the most robust findings, such as activation of the middle frontal gyrus and superior frontal gyrus was shown in high threat relative to low/absent threat situations. This was unexpected, given the link between prefrontal regions and lower threat levels supported in the systematic review. However, this is a restricted portion of the PFC and heterogeneity of threat type and task behaviour should be considered when interpreting this finding. Activation of the superior frontal gyri has been linked to attention and attention shifting (Nagahama et al., 1999), suggesting this region could be linked to general behaviour during active tasks of any description beyond the involvement of threat. Lateralization of region activation was apparent in the meta-analysis output, with high threat relating to greater activation of mostly right hemisphere regions and deactivation of the left side broadly speaking. This is in line with previous work linking the right hemisphere specifically to avoidant behaviour (Aupperle et al., 2015; Kirlic et al., 2017). Absence of activation of the PAG, midbrain, amygdala and hippocampus despite presence in individual studies and a focus on these areas in ROI analysis is notable. There are several important caveats to these findings: the number of studies included in the meta-analysis was small (Radua et al., 2012), making aspects of analysis potentially problematic (Radua et al., 2010), and the paradigms included maintained key differences (including consolidation of low-threat and non-threat against high threat). As such, further work with bigger samples and more consistent contrasts is required to build on this preliminary analysis.

Despite support for RST indicated in this review, self-report measures of RST systems (e.g. behavioural inhibition system/behavioural activation system response scale, BIS/BAS scale; Carver & White, 1994) were not shown to correlate with task behaviour or neural activation (Cunningham et al., 2011; Radke

et al., 2015); however, the trials using these measures were largely restricted to ROI analysis, and the BIS/BAS scales were designed under older RST models, before separation of fear (simple avoidance) and anxiety (goal-conflict) as independent systems (Jackson, 2009; McNaughton & Corr, 2004). Compatibility of self-report and behavioural assessment of defensive reaction has previously been questioned (LeDoux et al., 2017); comparison using updated self-report scales is a logical next step. Briefly considering the results of the present analysis with findings from a review of self-report fMRI-based studies identifies some areas of overlap, though notably the self-report trials had poor evidence of midbrain activation during imminent threat exposure (Shuhama, Blanchard, Graeff, & Del-Ben, 2017), which was a core finding in the active paradigm studies discussed here. This idea is explored further in the discussion chapter of this thesis (chapter 8).

Regarding individual differences, a role for trait-anxiety was highlighted in simple avoidance (Collins et al., 2014; Mobbs, Petrovic, et al., 2009; Rigoli et al., 2016), though only one goal-conflict trial found an association with behaviour (Loh et al., 2017). Both neuroticism and trait-anxiety were associated with amygdala and CC activity in response to threat (Mobbs et al., 2009). One study did focus on neuroticism, identifying that sub-types of neuroticism are associated with amygdala response to approach situations and negative stimuli (Cunningham et al., 2011). This latter result fits closely with speculation that overreaction to negative stimuli could underlie BIS reactivity (Barlow et al., 2014; Gray, 1982). Individual sensitivity to pain was shown to attenuate reward seeking, associated with the OFC and cerebellum (Talmi et al., 2009), and individual differences in approach or avoidant personality traits was associated with differential VTA and VS (i.e. motivational response; Haber & Knutson, 2010) activation during conflict (Gonen et al., 2016). Though not entirely unanimous (e.g. Aupperle et al., 2015), these findings highlight the importance of individual differences in understanding of both neural and behavioural defensive response, in line with contemporary views (Corr & Mobbs, 2018). As abnormal sensitivity to threat is considered a hallmark of anxiety disorders (Hundt et al., 2007; McNaughton & Corr, 2004) this is an important consideration. Further work is required to fully establish this line of thought, as few of the studies identified here monitored trait-level individual differences.

4.5.1 *Limitations*

Due to the small number of studies with appropriate data available, the presented meta-analysis relies on a limited amount of data and as such must be interpreted with caution. Similarly, this meant a sensitivity analysis regarding stimuli type or comparing naturalistic vs. conditioned threat was not possible. Many trials consistently used pre-defined ROIs, presenting findings from only one- or two-regions. This approach potentially ignores the wealth of data available from elsewhere and may preclude unexpected activations. ROI selection is also at risk of a strong publication bias. Publication bias is a concern in neuroimaging more broadly too, partly due to publications being based on effects in small samples (Jennings & Horn, 2012). Application of different toolboxes and statistical thresholds, limitations in sample sizes and resulting low statistical power can impact detection of true effects, replicability and consistency in the field (Acar, Seurinck, Eickhoff, & Moerkerke, 2018). The ‘file-drawer’ problem, in which findings that are not statistically significant are far less likely to be published, can be particularly compounded in meta-analysis, as significant findings are thus rarely contradicted (Acar et al., 2018). T-maps were available for 3 of the 5 studies included in this meta-analysis, which may reduce the risk of bias risk slightly. Egger’s test for publication bias was also adopted in this analysis, though this test is not always effective in meta-analyses with a small number of studies included. The results of this meta-analysis should be interpreted with caution, as the studies included were quite heterogeneous, often had small sample sizes and were few in number. Fear conditioning trials have a strong presence in the translational literature (Kirlic et al., 2017) and were included within this review; future work would benefit from comparison of defensive behaviour in response to conditioned vs. naturalistic threat. The paradigms identified in this review show considerable variability in design. Despite identification of 19 studies, the heterogeneity of tasks in this field is so high that meta-analysis of data was restricted to 5 data sets. However, conversely heterogeneity be helpful in identification of robust findings.

4.5.2 *Future directions in study design*

Several proposals are made for future paradigms. A paucity of work in anxious samples and its association with clinical understanding means comparative work between healthy and anxious samples

is a priority; moving research beyond anxiety is also of interest, as maladaptive defensive behaviours have also been highlighted as integral to disorders such as obsessive-compulsive disorder and autism (Gillan et al., 2014; Servatius, 2016). As aforementioned, neural activation during defensive behaviours in depression is unclear (Ferster, 1973; Marwood, 2017; Naragon-Gainey, 2010; Ottenbreit & Dobson, 2004), warranting further research within this diagnostic area. Only one study included freezing as a behavioural response, despite freezing being a core aspect of threat response system (FFFS) and common in rodent models. Development of paradigms able to support freezing as a legitimate response would enrich understanding of human fear and allow greater comparison with animal models. Given the association between experiments with high spatial components and hippocampal activation, care should be taken to avoid conflation; the use of joysticks to enlarge/shrink stimuli as a representation of approach/avoidance respectively (e.g. Radke et al., 2017, 2015; Cunningham et al., 2011) might be an alternative to maze/runway paradigms, though an assessment of potential spatial hippocampal involvement in this action is necessary first. However, maze paradigms remain faithful to the animal models that provided the basis for the field and provide opportunity for simple avoidance and goal-conflict trials within one task which provides greater insight.

Given the unexpected activation of frontal regions during higher threat shown in the meta-analysis, and the link between frontal gyri and attention (Nagahama et al., 1999) the potential confound of attention level should be considered in future work. Though activation is believed to change from forebrain-to-midbrain with threat proximity, the nature of this change is unknown. Prolonged threat exposure with gradual proximity change would indicate whether the change in activation is a binary switch or a gradual change; identifying the turning point would be useful, especially if combined with a measure of individual difference such as neuroticism. Identification of different cut-off points associated with neuroticism score would be informative considering the link between neuroticism and risk of anxiety disorders (Lahey, 2009).

The use of self-report and physiological data is inconsistent but recommended in future projects to represent participant experience of experimentally induced fear. State measures of anxiety or ongoing cardiac or skin conductance measures would be useful in tool validation (see Mobbs et al., 2007, 2009).

Very few studies have explored neuroticism in defensive behaviours, despite this being key in the theoretical literature (Barlow et al., 2014; Gray, 1982; McNaughton & Corr, 2004). There is evidence that alternate neural systems may be involved in the processing of monetary gain, relative to pain and affective threat outcomes (Kirlic et al., 2017). Some studies using monetary gain/reward also used physical threat stimuli such as electric shock (for example, Aupperle et al., 2015; Talmi et al., 2009), causing potential confounds. The immediacy of outcome of these stimuli may also be an issue, with immediate shock/emotionally aversive imagery not necessarily equivalent to promise of money later. In future exploration of an immediate and physical reward stimuli such as pleasant smells or sweet drinks/food would be beneficial, as attempted by (Rzepa, Fisk, & McCabe, 2017).

4.6 Conclusion

Generally, a change from cortical to subcortical activation is observed in response to increasing threat, whether the threat is being avoided or approached, whilst conflict is associated with an array of cortical and subcortical regions. The findings are largely in line with the predictions of RST, basic reward circuitry and motivational salience. The findings are also supportive of the close extrapolation from animal to human work that has shaped the field. Hippocampal involvement in simple avoidance appears largely associated with spatial demands, distinct from its role in goal-conflict trials. A meta-analysis of threat avoidance neural activation did not indicate activation of the same regions as the systematic review, though the limitations of this analysis are highlighted. There is a dearth of exploration in anxious populations, despite a theoretical focus on links between clinical presentation and threat sensitivity. Understanding the neural circuitry underlying common anxiety-related behaviours is key to the development and refinement of treatments for psychiatric conditions caused by dysregulation in these regions. There has been little consideration of individual differences in the research to date, which prevents conclusions from being drawn regarding neuroticism as a central factor in human defensive behaviour. Several recommendations for future paradigms are outlined.

Chapter 5: Effects of anxiolytic compounds on brain activation during defensive behaviours in a sample of high-neuroticism individuals with generalised anxiety disorder

5.1 Chapter summary

Generalized anxiety disorder (GAD) is the most frequently identified anxiety disorder in primary care, and is associated with substantial impairment, decreased work productivity and high economic burden (Wittchen, 2002). GAD is characterised by persistent and excessive worrying, tension, hypervigilance and somatic symptoms (Wittchen, 2002; Wittchen, Zhao, Kessler, & Eaton, 1994). Reinforcement Sensitivity Theory (RST) identifies threat sensitivity as the core of anxious psychopathologies (McNaughton & Corr, 2004), with some suggestion that neuroticism is integral to expression of this behaviour (Barlow et al., 2014; Gray, 1982). The initial aim of this experiment was to explore anxiolytic modification of neural activation during threat response in a sample of highly neurotic individuals with GAD, and to provide a comparison with the results of healthy controls indicated in chapter 4. Twenty-four participants were administered two variants of anxiolytics (a benzodiazepine and a cholinergic system modulator, the latter at two dosage-levels) and placebo, in a four-way crossover within-participant design. Participants completed self-report questionnaires and a human adaptation of the Mouse Defence Task Battery (Griebel, Blanchard, Jung, & Blanchard, 1995), the JORT (Perkins et al., 2013), to explore anxiety, neuroticism and threat response. In addition, the JORT has not previously been applied to a clinically anxious sample; pharmacological evidence is a common basis for the validity of anxiety-producing models (Korn et al., 2016), and as such validation of the JORT paradigm in a clinically anxious sample was an adjunct aim of this chapter.

Analysis indicated no significant effect of anxiolytic on neural activation during defensive behaviour. However, individual differences were shown to be key in anxiolytic effect on behavioural threat response: threat response was increased by benzodiazepines in participants with low fear-proneness (i.e. low fear-prone individuals responded more to threat after benzodiazepine administration) but decreased in higher scoring individuals (i.e. highly fear-prone individuals responded less to threat after

benzodiazepine administration). Of note, 'low' fear-proneness in this sample is likely higher than the general population, as the sample was selected for high neuroticism and GAD. Though no differences in neural activation were shown across conditions (simple avoidance vs. goal-conflict), fMRI analysis indicated increased anterior insula activation during chase (i.e. response to threat) relative to baseline phases. This is in line with previous work and the results of chapter 4, supporting claims that the insula is a core to anxiety sensitivity. Aberrant insula activation has also previously been linked to neuroticism (Paulus, Rogalsky, Simmons, Feinstein, & Stein, 2003; Stein, Simmons, Feinstein, & Paulus, 2007), though as the present sample was selected for high neuroticism scores caution should be applied when interpreting this finding in a wider context. Potential issues with the JORT paradigm are discussed, due to the lack of different behavioural during, and neural response to, threat- present vs. threat- absence in the task; in particular, distinguishing threat and non-threat trials in a highly anxious sample is a challenge for defensive behaviour tools.

This experiment was part of a larger experimental session. Findings from another emotional task completed at the same time have been submitted for publication in the journal of Translational Psychiatry (Wise et al, in Submission) in an article of which I am joint first author.

5.2 Introduction

Reinforcement sensitivity theory (RST; Gray, 1982; McNaughton & Corr, 2004) models defensive human behaviour across three orthogonal systems (Corr, 2004; Jackson, 2009). The Behavioural Activation System (BAS) controls approach towards appetitive stimuli, the Fight-Flight-Freeze System (FFFS) reacts to aversive stimuli with defensive avoidance, and the Behavioural Inhibition System (BIS) uses defensive approach to assess conflicting stimuli (Corr, 2004; Jackson, 2009; McNaughton & Corr, 2004). Though predicted to be distinct neuro-anatomically, the three systems functionally interact to elicit individual behaviour, appetitive response and mood (Corr, 2002, 2004; Hundt et al., 2007).

Psychopathology is thought to arise from hyper- or hypo- activity of these systems (Hundt et al., 2007). BIS hyper-activation is conceptually associated with anxiety disorders (Bijttebier, Beck, Claes, &

Vandereycken, 2009; Kasch, Rottenberg, Arnow, & Gotlib, 2002; Perkins et al., 2013) whilst the FFFS is linked to fear (Jackson, 2009) and fear-based pathologies, such as panic disorder (Bijttebier et al., 2009; McNaughton & Corr, 2004). RST-based behaviour is context-dependent; situations involving avoidable threat lead to simple FFFS activation, whereas the BIS responds to conflicting situations where threat must be approached (McNaughton & Corr, 2004). Abnormal BIS activation in anxiety disorders may lead to excessive avoidance behaviour, negative reinforcement and may impact therapeutic success due the importance of active engagement with threat in many interventions (LeDoux et al., 2017). As such, the FFFS and BIS formulate defensive behaviour response. There has been speculation that neuroticism lies at the root of the BIS and FFFS hierarchies, with abnormal function of these systems arising from the overreaction to negative stimuli associated with neuroticism (Barlow et al., 2014; Gray, 1982). As shown in chapter 4, despite the clear clinical implications of defensive behaviour all studies using functional imaging in active behavioural testing of simple avoidance and goal-conflict to date have recruited healthy participants. Similarly, little work has explored these behaviours in association with individual differences such as neuroticism.

Within RST, defensive distance (perceived distance from threat) is proposed to modulate neural activity of a functional hierarchy, moving from prefrontal/cortical regions during distal threat towards subcortical/midbrain regions as threat becomes more proximal (McNaughton & Corr, 2004; Mobbs, Marchant, et al., 2009). As shown in Figure 8, there is some evidence that threat avoidance via the FFFS may start in ventral prefrontal areas, moving through the anterior cingulate, amygdala, hypothalamus, to the periaqueductal grey as threat becomes closer (PAG; McNaughton & Corr, 2004). Defensive approach behaviours elicited by the BIS are proposed to begin in the dorsal prefrontal areas, moving through the posterior cingulate, septo-hippocampal system, amygdala, hypothalamus and PAG (McNaughton & Corr, 2004). There is a general agreement on this forebrain-to-midbrain switch during simple threat avoidance (Mobbs, Marchant, et al., 2009; Montoya et al., 2015; Wendt et al., 2017), as demonstrated in the systematic review in chapter 4. However, there is less of a clear consensus regarding goal-conflict, or activation in middle-range threat distance (as opposed to the extremities of distal and proximal threat) (Aupperle et al., 2015; Bach et al., 2014; Gonen et al., 2016; O'Neil et al., 2015).

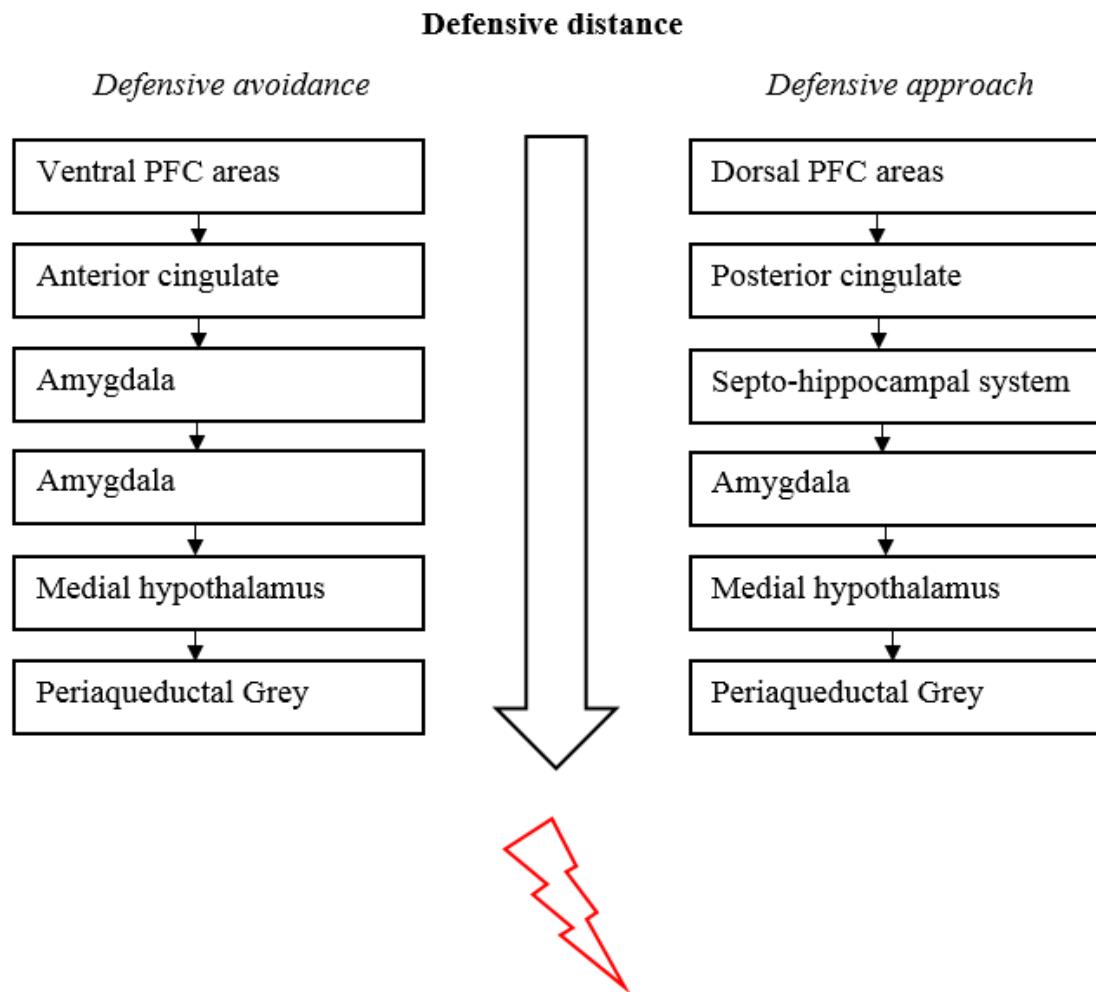


Figure 8 Forebrain-to-midbrain switch in neural activation hypothesised to occur with increasing threat proximity, adapted from McNaughton & Corr, 2004 and Mobbs et al, 2009. Lightning symbol represents threat, with distance from threat decreasing from top to bottom of the figure. PFC, prefrontal cortex

The Joystick Operated Runway Task (JORT; Perkins et al., 2010, 2013; Perkins, Kemp, & Corr, 2007) utilizes a virtual predator paradigm in a human translation of the Mouse Defence Test Battery (MDTB; Griebel, Blanchard, Jung, & Blanchard, 1995). The JORT requires physical force from participants to avoid or approach threat, imitating real-world experience extrapolated from rodent models. Previous work with this tool has indicated benzodiazepine modulation of risk assessment intensity (Perkins et al., 2009) behaviour, though no effect was indicated in threat avoidance. Specifically, benzodiazepine administration decreased risk assessment in individuals with high scores in fear-proneness whilst the

reverse was shown in low scorers. Further, both self-reported fear-proneness and threat avoidance behaviour as measured by the JORT were elevated in healthy participants who had been identified post-hoc as having a genetic risk factor for panic disorders, relative to participants without the same risk (Perkins et al., 2010).

The clear link between defensive behaviour and psychiatric disorder is indicative of domain-based pathology (Bijttebier et al., 2009; LeDoux et al., 2017) and shows the potential trans-diagnostic function in anxiety and clinical potential of the paradigm. However, to date there has been a distinct lack of exploration in clinically anxious individuals. Further, the JORT has not been applied to clinically anxious samples in an fMRI paradigm.

Pharmacological evidence is a common basis for the validity of anxiety-producing models (Korn et al., 2016). Previous work has largely focused on benzodiazepines, despite their association with psychomotor slowing (Longo & Johnson, 2000), without exploration of alternative classes of anxiolytic. Cholinergic antagonists have shown anxiolytic properties in rodents (Sienkiewicz-Jarosz et al., 2000) and have been associated with prevention of fear renewal after extinction in humans (Perusini & Fanselow, 2015; Zelikowsky et al., 2013). Nicotinic acetylcholine receptors (nAChRs), especially the α -7 receptor, have been linked to anxiolytic behaviour in rodents (Mineur et al., 2016) potentially mediated by the amygdala (Séguéla, Wadiche, Dineley-Miller, Dani, & Patrick, 1993). As such, cholinergic modulators are interesting anxiolytic candidates for comparison with the standard benzodiazepine approach. The nAChRs modulator used in this study indicated efficacy in animal models of anxiety and has also been evaluated in Phase I trials indicating it is safe and well tolerated. Though the animal data is unpublished at present, a paper outlining an exploration of response to emotional faces after administration of this compound is currently in submission (Wise, Patrick, Meyer, Mazibuko, Oates, van der Bijl, Danjou et al, In Submission).

5.3 Aims & hypotheses

This study aims to address the question of fear- and anxiety- related neural and behavioural systems with a novel approach. In line with this previous work, (both) anxiolytic medications were expected to

reduce threat avoidance (as previous results from the JORT relied on healthy controls), increased threat approach and to reduce self-reported anxiety, relative to placebo. Neurally, a forebrain-to-midbrain change was expected in the form of:

1) Midbrain/PAG activation during peak threat (McNaughton & Corr, 2004; Mobbs et al., 2009; Montoya et al., 2015; Wendt et al., 2017)

2) PFC activation during anticipation (i.e. distal threat) (McNaughton & Corr, 2004; Mobbs, Marchant, et al., 2009; Mobbs et al., 2007)

3) In line with chapter 4, septo-hippocampal involvement in goal-conflict conditions was also expected (McNaughton & Corr, 2004); however, as the JORT involves a considerable level of spatial movement, this activation is predicted to also be present in simple avoidance, again in line with the findings of chapter 4.

5) These activations were expected to be lower in the anxiolytic conditions relative to placebo, indicative of a reduction in fear and anxiety.

5.4 Materials & methods

5.4.1 Participants

Individuals meeting DSM-IV criteria (American Psychiatric Association, 2013) for GAD assessed with the Mini International Neuropsychiatric Interview (MINI, Version 5.0; Sheehan et al., 1998) were recruited from the Greater London area through advertisements in King's College London email circulars and websites open to the general public. Participants completed an online version of the Trait Self-Description Inventory (TSDI; Collis & Elshaw, 1998) and were selected for telephone screening if they scored more than 1 standard deviation above average on trait neuroticism (score ≥ 64 for females, ≥ 58 for males) as this factor is associated with risk of clinical anxiety (Lahey, 2009). Participants were screened by a psychiatrist and excluded based on physical or additional mental health disorders (co-morbid social anxiety was permitted). Participants were excluded if they scored ≥ 15 on the Montgomery-Åsberg Depression Rating Scale (MADRS; Montgomery & Åsberg, 1979) to minimise

co-morbid depression in the sample. Participants were excluded if they had smoked within last three months, and were required to have no uncorrected visual problems, neurological disorders or learning disabilities, and to have fluent English. Further information can be found in chapter 2.

5.4.2 *Materials*

5.4.2.1 The Joystick Operated Runway Task

The JORT (Perkins et al., 2009) has two trial types, measuring simple avoidance (flight intensity, FI) and goal-conflict (risk assessment intensity, RAI) in response to threat of a mild electric shock (see Figure 9). Participants are in control of a green dot on screen, which they must keep away from the threat indicator (a red dot, which may administer a mild electric shock if touched). In order for the green dot to remain visible on screen at all times, it actually remained motionless in the centre of the runway whilst the background scrolled downwards to create a visual impression of speed/movement. Participants use a force-sensitive hand gripper to control the green dot, squeezing tighter increased velocity in proportion to the pressure applied to the gripper. At the start of simple avoidance trials, the chasing predator (red dot) would approach the agent (green dot) from the bottom of the screen (appearing from off-screen initially), forcing the agent to accelerate to an escape velocity. In the goal-conflict trials the chasing predator would also approach the agent to force the green dot to accelerate, but a second red dot would then appear onscreen (ahead of the green dot). The speed of the preceding red dot (in both simple avoidance and goal-conflict trials) varied to ensure it remained on screen, whilst the top red dot (only present in the goal-conflict trials) was kept constant (i.e. did not accelerate in line with acceleration of the green dot, nor disappear off the top of the screen). The gripper is calibrated to a force requirement of 7.5kg. To control for participant motor functional ability trials were conducted with and without threat, as signalled by presence or absence of a lightning bolt icon on screen. FI is calculated as increased velocity of escape from a pursuing red dot when the lightning flash icon is present, relative to when it is absent. RAI is calculated as forward-backward oscillations (measured as the standard deviations of the average speed of movement of the green dot) when attempting to remain safely between the two red dots in the presence of the lightning flash icon, relative to when the icon is

absent. This aims to replicate avoidance and exploratory movements made by rodents in animal models (Griebel, Blanchard, Agnes, & Blanchard, 1995).

Each testing session involved 48 intermixed trials (12 of each type, i.e. simple avoidance with threat and without threat, goal-conflict with threat and without threat). Trial intervals ranged in length from 15 to 30 seconds in a pseudorandomised order promote unpredictability of escape duration. Following capture by a red dot, the participant experienced a mild electric shock (at a level pre-chosen by each participant individually to be aversive but tolerable, due to the length of the experiment) to their foot, followed by termination of trial. If the threat was avoided for the duration of the trial (7 seconds of threat exposure), the trial terminated at the end of the period. To prevent early capture resulting in accelerated progress through trials, it was followed by a period of inactivity on screen to maintain preprogrammed trial lengths. Participants were given a practice session prior to administration at each study visit. The total task length was around 18.5 minutes.

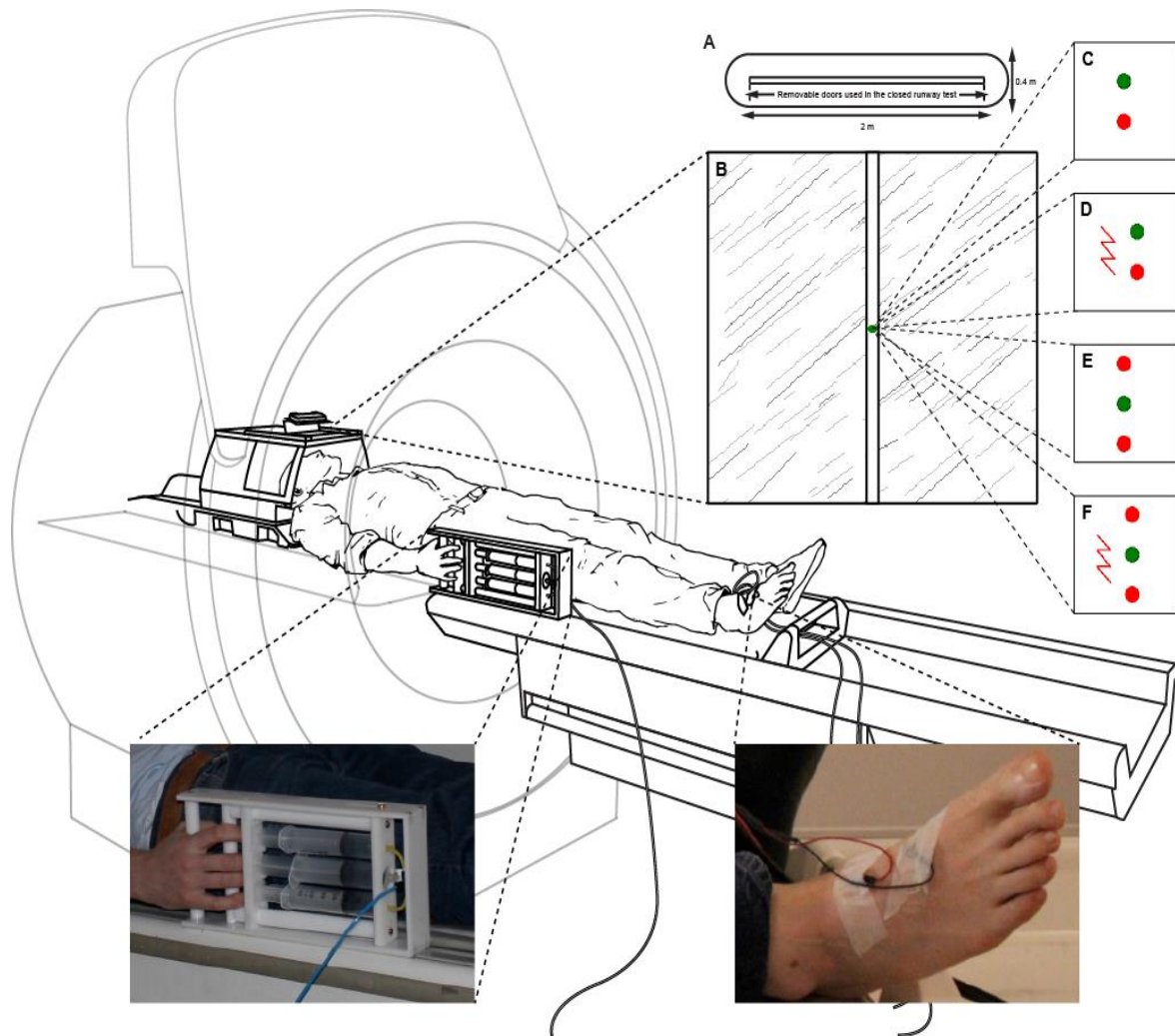


Figure 9 JORT human translational measure of active avoidance (b:f), based on the Mouse Defence Test Battery (a): a) runway section; b) participant visual field c) FI, no threat; d) FI, threat present; e) RAI, no threat; f) RAI, threat present. JORT, joystick operated runway task; FI, flight intensity; RAI, risk assessment intensity

5.4.2.2 The Fear Survey Schedule (FSS)

The FSS (Wolpe & Lang, 1969, 1977) 108-item self-report questionnaire exploring sources of negative emotional reactions and fear-proneness. Potentially fear-provoking items are listed, and participants respond with how much that item disturbs them on a scale of 0-4 (not at all – very much).

5.4.2.3 The Hamilton Anxiety Rating Scale (HAM-A)

The HAM-A (Hamilton, 1959) An observer-rated, 14-item measure of anxiety-related behaviours, in which the observer rates individuals on a scale of 0-4 (not present – very severe).

5.4.2.4 The Montgomery-Åsberg Depression Rating Scale (MADRS)

A clinician rated measure of current (previous 2 weeks) depressive symptomology, the MADRS (Montgomery & Asberg, 1979) rates individuals from 0-6 on 10 items (e.g. ‘apparent sadness’).

5.4.2.5 The Spielberger State-Trait Anxiety Inventory (STAI)

The STAI (Spielberger et al., 1970) is a two-form self-report measure of state and trait anxiety, requiring response to positive and negative thoughts and beliefs, using a Likert scale of 1-4 (almost never – almost always).

5.4.2.6 Dread self-rating scale

A visual analogue scale measuring dread experienced, rated from 0-100 (no dread- complete dread).

5.4.2.7 The Trait Self-Description Inventory (TSDI; Collis & Elshaw, 1998)

Participants completed a 50-item version of the TSDI, a self-report measure of the Big-5 personality traits. Participants respond using a Likert scale to a series of questions and adjectives.

5.4.3 *Procedure*

This study was a 4-way crossover, double-blind randomised controlled trial. Participants attended 4 study visits, experiencing the interventions in a randomised order. The novel compound, BNC210, was administered at high (BNC high; 2000mg) and low (BNC low; 300mg) doses (as this was part of a wider experiment exploring optimal dosing, see Wise et al, in submission), along with lorazepam at 1.5mg and a placebo. Study visits were spaced a minimum of 5 days apart, to ensure pharmacological washout. Participants ate a standardised breakfast on the day of the visit and avoided caffeine for 12 hours prior to the visit. As the absorption rates of BNC210 and lorazepam differ, the dosing schedule and placebo administration was manipulated by incorporating two dose administrations per visit to maintain the double-blind (Figure 1, chapter 2).

Participants completed the JORT as part of a wider series of MRI and fMRI experiments not reported here (see Wise et al., in submission). The STAI was completed 3 times per visit: prior to dosing, prior

to JORT administration and prior to discharge. HAM-A, MADRS and FSS data were collected at the initial screening visit, which took place ≤ 6 weeks prior to first dosing (Figure 10).

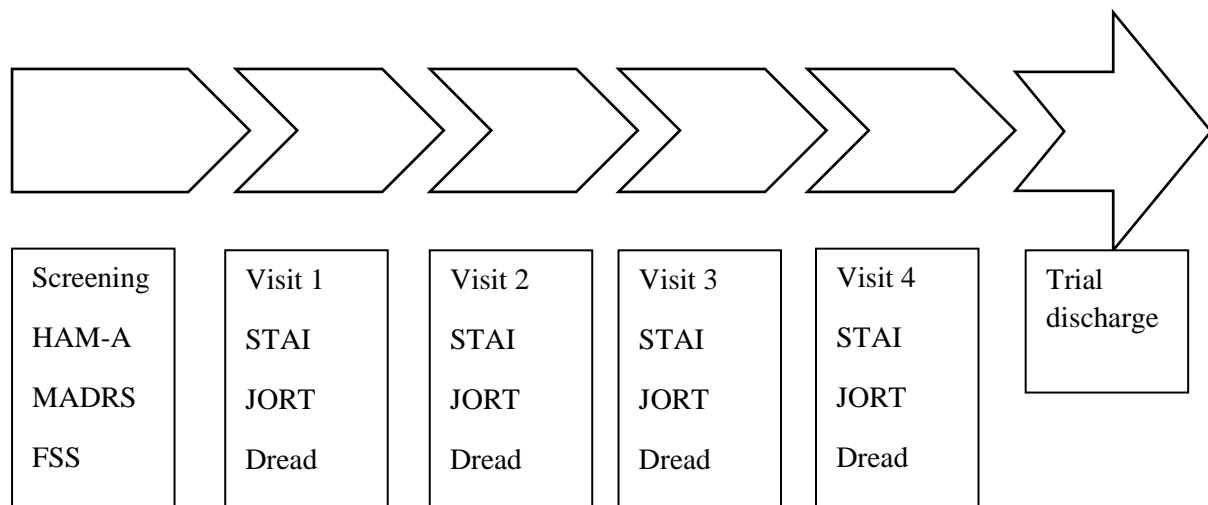


Figure 10 Measures at each time point, throughout trial. HAM-A, Hamilton Anxiety Scale; MADRS, Montgomery-Asberg Depression Rating Scale; FSS, Fear Survey Schedule; STAI, State-Trait Anxiety Index; JORT, Joystick Operated Runway Task; Dread, dread self-rating scale.

5.4.4 Behavioural data analysis

SPSS (IBM, Chicago, U.S.) was used in the behavioural analysis. One-way ANOVA were conducted to assess differences between drug conditions for FI, RAI, speed (simple avoidance trials), oscillations (goal-conflict trials) and number of times caught (both trial types) for threat vs. non-threat. Differences in STAI scores from pre-dosing to pre-task were assessed with paired-sample t-tests. An ANOVA explored the role of fear-proneness in JORT behavioural output during exposure to anxiolytics. Regression analysis was conducted to explore variance in FI and RAI in each condition with pre-task STAI scores.

Speed and oscillations are included as measures of behaviour in threat vs. non-threat scenarios in addition to FI and RAI, which require threat and non-threat combined.

5.4.5 Functional MRI acquisition

Data was acquired using a GE MR750 3-Tesla MRI scanner, with a 12-channel head coil. 180 volumes were collected in each functional run, following a T2*-weighted echo-planar imaging sequence

(TR=2000, TE=30ms, FOV=22.1cm, 41 slices, at resolution 3.3mm³). The initial 4 volumes were removed to control for magnetisation equilibration effects. Volumes were acquired sequentially, top-to-bottom ordered. High resolution T1-weighted structural scans were also acquired for each participant (TR=7.31, TE=3.02, 196 slices at a voxel size of 1.2 x 1.05 x 1.05 mm). Scanning took place 5 hours post first dose; the JORT measure came last in a sequence of MRI and behavioural tools, around 1-hour post scan start.

5.4.6 *Functional MRI pre-processing*

All data was pre-processed in SPM12 (<http://www.fil.ion.ucl.ac.uk/spm>) with Nipype scripts (<http://nipy.org/nipype/>) and additional custom code developed by Dr Toby Wise. Images were realigned to the initial image of the run, with slice timing corrected and co-registered to the individual's T1 image. Segmentation and normalisation were conducted on the T1 images, with deformation fields then used for normalisation of functional images to MNI space. Images were smoothed with a 6mm FWHM kernel. Considering the potential for movement in this experiment, realignment parameters and volume-to-volume signal intensity changes were identified using ArtifactDetect (through Nipype) and subjects showing transition of over one voxel (3mm) were removed from analysis. In order to provide extra security against motion-related artefacts in the data (considered particularly important as painful stimuli may cause involuntary movement), a component based method (CompCor; Behzadi, Restom, Liau, & Liu, 2007) was included. CompCor involves a principle component analysis using signal derived from noise ROIs (specifically, white matter and cerebral spinal fluid voxels) to identify 6 components which represent non-neural signals. These can then be included in the first level models to reduce the impact of physiologically associated noise and movement.

5.4.7 *Functional MRI analysis*

5.4.7.1 First-level analysis

As with pre-processing, first level analysis was conducted using SPM12 and custom scripts/code developed by Dr Toby Wise. Anticipation (period prior to chase, when trial type is cued; 6 seconds), chase (active avoidance of threat; ≤ 7 seconds) and the inter-trial interval (period after chase, when the

participant has either escaped or received electric shock, prior to initiation of next trial; 1-6 seconds) were included as regressors across trial types (see Figure 11, below)

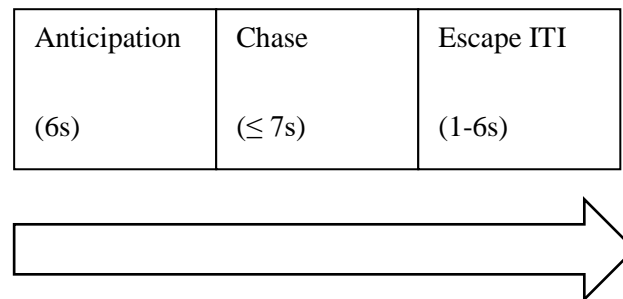


Figure 11 JORT experimental paradigm timeline. S, seconds; ITI, Inter Trial Interval.

Cumulative threat (area under the curve of participant distance from closest chasing stimuli, representing velocity and distance travelled during movement away from threat), peak threat (closest distance to either chasing stimuli during chase) and oscillation amplitude (standard deviations of the average speed of movement of the green dot between a preceding and pursuing threat) were included as parametric modulators.

Occasionally, technical faults with the force-sensitive hand-gripper caused absence of recorded reaction from the participant. In these cases, the trial was excluded by inclusion as a nuisance regressor in the model; in situations where more than four trials in any one condition were unusable the participant was excluded from analysis (this was also applied to behavioural analysis to ensure compatibility).

5.4.7.2 Second-level analysis

Main task effects were evaluated in the placebo condition to identify system involvement in active avoidance and approach-avoidance behaviour without anxiolytic influence. Task condition (anticipation, chase) were compared to baseline activity (pre-task cross fixation) and the main-effects of 1) trial-type (simple avoidance vs. goal-conflict); 2) threat (threat vs. no threat) were analysed. During the chase phase, neural activity at peak threat (activity during chase correlated to distance from red dot), cumulative threat and oscillation level was analysed. Neural activation was then compared

between each anxiolytic (lorazepam, BNC low, BNC high) and placebo using paired-sample t-tests. Age and gender were controlled for throughout.

The role of individual differences in pre-task anxiety (STAI), FFS total score and post-task reported dread in neural activation were explored with multiple regression. As participants were selected for high neuroticism levels this was not included as a regressor.

Whole-brain analysis were conducted with voxelwise thresholding of $p < .001$, and cluster-level thresholding at $p < .05$, family-wise error (FWE) corrected; these thresholds have previously been identified as providing appropriate control for false positives (Eklund, Nichols, & Knutsson, 2016). Masks were applied with a threshold of $p < .05$. ROI masks (midbrain, PFC and hippocampus) were generated using the WFU-PickAtlas toolbox (Wake Forest University) using automatic anatomic labelling (AAL); the PAG was defined using co-ordinates outlined in the literature (MNI co-ordinates $x = 4$, $y = -30$, $z = -24$, with a 6mm radius ; Mobbs, Marchant, et al., 2009; Mobbs et al., 2007), though the lack of explanation in how this location was selected in the original papers is a potential issue.

5.4.7.3 Power calculations

The minimum number required to achieve a suitable level of power to explore differences in behavioural output between conditions was calculated using G*Power (Faul, Erdfelder, Buchner, & Lang, 2009; Faul, Erdfelder, Lang, & Buchner, 2007) as 15 individuals to identify large effect sizes ($d = 0.7$, $\alpha = .05$ and power = .80), and 45 to identify moderate effect sizes ($d = 0.7$, $\alpha = .05$ and power = .50). Accurate and consistent methods of meaningful power calculations in neuroimaging studies are still in their infancy, but previous studies have recruited around 24 participants for repeated measures analysis of pharmacological fMRI data in affective disorders broadly (Takahashi et al., 2005) and GAD specifically (Sheline et al., 2001).

5.5 Results

5.5.1 Behavioural results

Demographic data for the sample is presented in Table 12 including questionnaire data: 24 (21 female) participants were recruited (mean age 23.6, SD \pm 6.53). One participant was excluded from all conditions due to unusable fMRI data. Four participants were removed from the placebo condition due to head movement ($n = 2$) or unusable behavioural data due to technical issues with the joystick in more than 4 trials per participant (see section 5.4.7.1 for more detail; $n = 2$). Due to the contrasts used in the fMRI analysis the four participants removed from placebo were also removed from the drug conditions. Therefore, six participants were removed from the lorazepam condition (4 placebo), and four from each of the BNC210 conditions (all placebo).

Table 12

Basic demographic information and screening stage psychiatric data

			HAM-A	MADRS	FSS	STAI*
	N (female)	Age (SD)	M (SD)			
Placebo	19 (18)	22.84 (7.0)	17.26 (10.3)	8.61 (3.7)	117.1 (58.3)	39.2 (10.9)
Lorazepam	17 (16)	23.18 (4.1)	16.88 (10.7)	8.5 (3.4)	110.1 (57.7)	39.55 (9.1)
BNC Low	19 (18)	22.84 (4.0)	17.26 (10.3)	8.6 (3.6)	117.1 (58.3)	37.4 (7.48)
BNC High	19 (18)	22.84 (4.0)	17.26 (10.3)	8.6 (3.6)	117.1 (58.3)	37.4 (7.48)

* Pre-scan (post-dose) time-point

HAM-A: Hamilton Anxiety Rating Scale; MADRS: Montgomery-Asberg Depression Rating Scale; FSS: Fear Survey Schedule; STAI: State-Trait Anxiety Inventory; M: mean; SD: standard deviation.

Average FI, RAI and number of times caught were calculated per condition are shown in Table 13, below.

Table 13

Average (mean) FI, RAI and number of times caught, by condition and threat presence

	FI	RAI	Caught, simple avoidance		Caught, goal-conflict	
			Threat	Non-Threat	Threat	Non-Threat
	M (SD)		M (SD)		M (SD)	
Placebo	.225 (.61)	.045 (.32)	.00 (.00)	.32 (1.2)	4.89 (4.2)	5.00 (3.4)
Lorazepam	.061 (.67)	-.119 (.34)	.47 (.80)	.59 (1.4)	7.18 (3.1)	7.82 (3.3)
BNC Low	.074 (.44)	-.054 (.31)	.16 (.38)	.26 (.73)	5.26 (3.2)	6.0 (2.6)
BNC High	.352 (.01)	.927 (.28)	.79 (2.5)	1.26 (2.8)	4.47 (3.9)	5.21 (3.8)

FI: flight intensity; RAI: risk assessment intensity; M: mean; SD: standard deviation

One-way ANOVA assessed difference in simple avoidance behaviour (FI), goal-conflict (RAI), oscillations in goal-conflict, speed of escape in simple avoidance and the number of times participants were caught (in both trial types, and in total) across drug conditions. No significant difference was observed in any of these factors (all $p > .05$). For completeness (and in line with statistical methodology of the fMRI analysis), paired-samples t-tests were also conducted to explore whether there were significant differences between placebo and each of the drug conditions (lorazepam, BNC Low and BNC High). No significant difference was observed between placebo and any of the drug conditions, in FI or RAI (all $p > .05$). A follow-up multivariate regression in which gender was controlled for also revealed no significant effects (all $p > .05$).

The role of fear-proneness (threat magnitude; FSS) was explored across conditions. Though no significant interaction was shown for the tissue-damage subscale (all $p > .05$), a significant relationship in the lorazepam condition between full-scale FSS scores and both FI ($f(15) = 246.4$, $p = .05$) and RAI ($f(15) = 3245.6$, $p = .014$) was shown. To explore this further, the FSS scores were split using the sample average and behavioural output across conditions plotted (Figure 12). Lorazepam increased FI

and RAI in low scorers but decreased both in high scorers. Division of FSS scores by average is for illustrative purposes, the interaction was analysed using scores as a continuous variable.

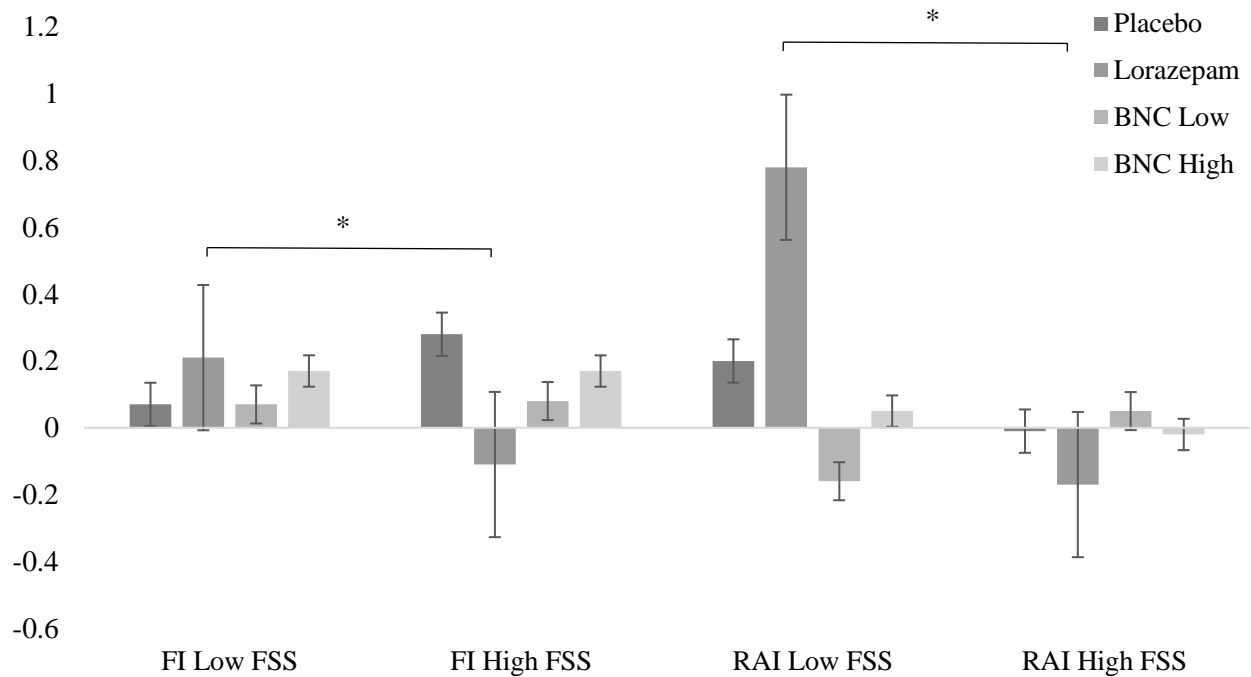


Figure 12 FI and RAI (mean) average scores, with population divided in to high and low FSS scorers (placebo, $n = 19$; Lorazepam, $n = 17$; BNC Low, $n = 19$; BNC High, $n = 19$)

To assess the subjective experience of anxiety throughout the experiment, paired-samples t-tests were also conducted to compare pre-dose and pre-scan self-reported STAI score. A significant reduction was observed in placebo ($t(19) = 2.547, p < .05$), BNC low ($t(19) = 2.985, p < .05$) and BNC high ($t(19) = 2.246, p < .05$), but not lorazepam ($p = .258$). Regressions were used to explore the role of pre-scan STAI in FI and RAI behavioural outputs. No significant interactions were observed (all $p > .05$). This procedure was repeated with pre-scan STAI and velocity in the simple avoidance trials or oscillation magnitude in the goal-conflict trials, but no significant interactions were observed ($p > .05$).

5.5.2 Functional MRI results

5.5.2.1 Task effects

No significant activation was identified during anticipation vs. baseline (fixation cross) across trial types, when thresholded at $p < .001$, though a trend towards significance was observed in the left precentral gyrus. There was no significant effect of threat (present vs. absent) or of trial type (simple avoidance vs. goal-conflict trials) in the anticipation phase. Heightened activity in the anterior insula (bilaterally; Figure 13) left central operculum and left inferior occipital gyrus was observed during flight (chase phase), relative to baseline; see Table 14 for further details. No effect of threat or trial type was present in the chase phase. Directionality of relationships were confirmed using t-tests.

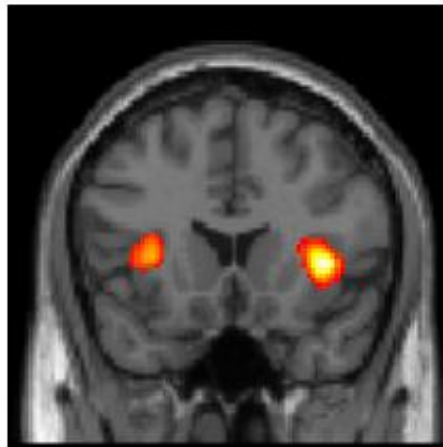


Figure 13 Bilateral anterior insula activation shown during flight; figure created using MRICron and SPM

ROI analysis used pre-determined masks from the WFU PickAtlas. A frontal lobe mask was applied in the anticipation phase to capture PFC response to distal threat, though no significant activation was detected. Similarly, no effect of proximal threat (i.e. during the chase phase) was observed when midbrain mask was applied, nor a mask modelled from Mobbs and colleagues' analysis of PAG activation (MNI space co-ordinates $x = 4$, $y = -30$, $z = -24$, with a 6mm radius; Mobbs et al., 2009). As planned, a mask of the bilateral hippocampus was applied to comparisons of goal-conflict and simple

avoidance trials in both anticipation and chase phases of the experiment, though no significant activation was identified.

Post-hoc analysis was conducted to assess whether significant differences were present in brain activity after escape from threat compared to escape from non-threat, across trial types. Whole-brain level analysis revealed a significantly greater activation in the bilateral anterior insula after escape from threat, relative to non-threat (see Table 14).

Table 14

Neural activation indicated by whole-brain analysis during anticipation, flight, oscillation (RAI) and escape

Brain region	MNI Peak co-ordinates	p	f	Direction
Anticipation (across trial types & threat presence)				
Left Precentral Gyrus	-42, -8, 50	.005	80.65	Task > baseline
Flight (across trial type & threat presence)				
Right anterior insula	38, 18, 2	<.001*	266.32	Task > baseline
Left anterior insula	-32, 18, 6	<.001*	139.66	Task > baseline
Left central operculum	-48, 2, 2	<.001*	202.89	Task > baseline
Left inferior occipital gyrus	-42, -68, 0	<.001*	150.52	Task > baseline
Right superior parietal lobule	20, -64, 58	.002	95.13	Task > baseline
Oscillation during flight (across trial type)				
Right supramarginal gyrus	60, -38, 34	<.001*	309.83	Task > baseline
Left inferior occipital gyrus	-42, -68, 2	<.001*	224.08	Task > baseline
Right supplementary motor cortex	-6, 8, 44	<.001*	203.21	Task > baseline
Left anterior insula	-38, 16, -4	<.001*	187.66	Task > baseline
Right superior parietal lobule	20, -62, 58	<.001*	173.72	Task > baseline
Right central operculum	46, 2, 8	<.001*	158.17	Task > baseline
Right supramarginal gryus	38, -30, 40	<.001*	154.31	Task > baseline
Right precentral gyrus	54, 8, 38	<.001*	144.50	Task > baseline
Left thalamus	-16, 20, 4	.001	113.16	Task > baseline
Left superior frontal gyrus	-2, 58, 0	.001	109.66	Task < baseline
t				
Left middle cingulate gyrus	-6, 8, 44	<.001*	14.26	Task > baseline

Brain region	MNI peak co-ordinates	p	f	Direction
Escape (from threat vs. non-threat, across trial type)				
Right anterior insula	38, 18, 2	<.001*	266.32	Threat > non-threat
Left anterior insula	-32, 18, 6	<.001*	139.66	Threat > non-threat
Left central operculum	-48, 2, 2	<.001*	202.89	Threat > non-threat
Left inferior occipital gyrus	-42, -68, 0	<.001*	150.52	Threat > non-threat
Right superior parietal lobule	20, -64, 58	.001	95.13	Threat > non-threat
* Significant at threshold of $p < .001$; activations up to $p = .005$ are included for reference.				

There was also no significant effect of peak threat (i.e. activation during chase did not correlate with participant's green dots proximity to red dot threat(s)) or cumulative threat (i.e. threat throughout chase). However, a significant effect of oscillation (standard deviations of the average speed of movement of the green dot between a preceding and pursuing red-dot threat) in several regions was observed (Table 14), including the anterior insula.

5.5.2.2 Drug effects

Whole-brain analysis revealed no significant effects of drug (lorazepam, BNC210 low or BNC210 high) in neural activation during the task when compared to placebo. This included absence of effect of threat presence and trial type in anticipation or chase phases. There was no significant effect associated with peak threat, cumulative threat or oscillation in any of the three drug conditions, relative to placebo. A one-way ANOVA indicated no significant difference in head movement between included participants in the 4 conditions ($p = .538$).

5.5.2.3 Self-reported anxiety

Multiple regression of self-report data against neural activation revealed no significant interaction with FSS (measured at screening visit), STAI (pre-scan) or dread rating (post-scan) in any condition. As participants were selected for high neuroticism, this factor was not included in regression analysis.

5.6 Discussion

This experiment investigated neural activation in highly neurotic individuals with GAD during expression of defensive behaviours in response to threat. Though activation of the anterior insula, operculum (covering the insula; Chen et al., 1996), supramarginal gyrus, superior parietal lobe and inferior occipital gyrus was observed, contra to all hypothesis there was no activation of the forebrain during anticipation (i.e. distal threat) or PAG and midbrain during peak (i.e. proximal) threat, nor was the hippocampus or septo-hippocampal system activated. Further, administration of anxiolytics had no direct effect on behaviour or neural activation during the task.

Self-reported fear-proneness (threat magnitude) as measured by the FSS was associated with differential effect of lorazepam at a behavioural level. In an expansion and partial replication of previous work (Perkins et al., 2013) lorazepam was associated with increased flight intensity during simple avoidance in individuals with low fear-proneness, but with decreased flight intensity in those with high levels. This was replicated in goal-conflict trials. Parallels have been drawn between human trait- and rodent state- individual differences in anxiety, with anxiolytics shown to reduce RAI behaviour in rodents experiencing mild threat, and increase RAI during more severe threat (Blanchard & Blanchard, 2008; Perkins et al., 2013). This is in line with RST, which proposes that trait individual differences modulate reactivity of the BIS and FFFS (Corr, 2004; McNaughton & Corr, 2004). This finding has relevance to clinical work, as administration of benzodiazepine treatment may have contraindications for those individuals with lower-end threat magnification. It should be noted that ‘low’ threat magnification in this sample is still likely quite high, given their GAD diagnosis and high levels of neuroticism.

No other significant effect of drug was observed. As drug effects were demonstrated in another emotional task in the same fMRI series, both BNC210 and lorazepam have confirmed anxiolytic properties in this sample (Wise et al., in submission). It is possible that the JORT was completed past peak drug activation, as the other tasks were performed first. Further, due to issues with head movement a number of participants were excluded, which may have led to issues in achieving adequate power. Conversely, there may be problems with the paradigm; this idea is supported by the lack of difference in neural activation between conditions, contra to the predictions of RST (McNaughton & Corr, 2004).

The inability to maintain threat-naivety in human participants and the importance of context in human defensive behaviour (Corr, 2013) may have resulted in sustained anxiety throughout the experiment (as the entirety becomes a defensive approach scenario; Perkins et al., 2013). Threat may never be ‘distal’ resulting in poor differentiation of defensive distance, particularly in the present highly neurotic sample.

Similarly, there was no evidence of a switch from distal to proximal threat during the task, which may reflect experience of sustained anxiety throughout. Theoretically, absence of this switch could reflect a disrupted mechanism in GAD, particularly considering most of the previous work that has identified the switch has focused on healthy controls (see chapter 4). Abnormal functioning of limbic-prefrontal circuitry during processing of threatening (Monk et al., 2006) and emotional (Etkin, Prater, Hoefft, Menon, & Schatzberg, 2010) stimuli is considered typical in GAD, and anxiety more broadly (for overview: Bishop, 2007). As activity in these regions was not observed in this experiment, it is unlikely that the activation demonstrated here is representative of what might be expected during processing of threat by individuals with GAD. It is possible that the lack of activation in these expected regions is due to paradigm issues (see below for discussion of this point) or low sensitivity in the analysis. As no average or low neuroticism scorers or healthy controls were included, it is not possible to draw more concrete conclusions on this matter presently. Further work is required to directly compare individuals with GAD and healthy controls, as well as exploring varied neuroticism levels and utilizing additional, well-validated, paradigms.

Experience of high levels of sustained threat throughout experimental settings is potentially magnified in anxious individuals, as sustained fear is associated with clinical anxiety (Davis et al., 2010). This may also explain the lack of differential neural activation in threat vs. non-threat trials as presence of threat periodically throughout with no prolonged ‘safe’ period may promote sustained fear across the whole paradigm. The literature suggests that individuals with clinical anxiety are more sensitive to contextual fear, as created by the use of threat cues (Grillon, Dierker, & Merikangas, 1998), and that the exaggerated contextual fear shown in anxiety may cause assumption of threat presence even when cue is absent (Klein & Seligman, 1976). However, the amygdala activation that would be expected in such a scenario was not shown here. An alternative explanation is that the threat presented is not

adequately threatening, though electric shocks have previously been used successfully to trigger defensive behaviour (for example, Mobbs et al., 2009, 2007).

No neural differences were observed between trial types (simple avoidance vs. goal-conflict trials). Previous work investigating goal-conflict has typically presented participants with conflict around approaching a reward that is paired with a probabilistic threat (Bach et al., 2014; Gonen et al., 2016; Schlund et al., 2016; Talmi et al., 2009). The hippocampal system is thought to play a role in decision making in response to valuation of potential outcomes (Kirlic et al., 2017). The JORT instead requires avoidance of two threats (of equal ‘value’) which would suggest that success in this trial type is more accurately associated with relief of non-punishment (Corr, 2002; McNaughton & Corr, 2004). The original rodent models from which the JORT was developed involve approach-avoidance in goal-conflict scenarios as a way for the subject to gather information (Blanchard, Griebel, & Blanchard, 2003; Perkins et al., 2009). Absence of tangible reward or information-gain in the JORT may explain the lack of neural differentiation between our simple avoidance and goal-conflict trials, and absence of hippocampal activation in the goal-conflict trial. Further, participants do not have a choice in behaviour, causing absence of actual decision-making.

Heightened activation of the anterior insula was observed in flight- from and escape- from threat, relative to non-threat. This reflects the diverse roles attributed to the anterior insula, which includes integration of external threatening stimuli with internal perception (Paulus & Stein, 2006). This area has also been associated with defensive behaviour involving pain-based threat (Talmi et al., 2009). As an area with bidirectional connections to the amygdala and orbitofrontal cortex, the insular cortex is in a relay position regarding stimuli salience, and is potentially responsible for understanding how stimuli may impact bodily state (Paulus & Stein, 2006). As the JORT does not divide trials in to safe and not-safe blocks, it is possible that there is continued concern over imminent pain (considering each non-threat trial only provides 20 seconds of pain-free context), which would also be reflective of potentially exacerbated sustained anxiety throughout the entire paradigm, as discussed above. However, there was a significant difference in anterior insula activation in escape from threat vs. non-threat suggesting a degree to awareness of threat absence, after successful avoidance at least.

Heightened insular activity has been proposed as a neuroanatomical candidate for anxiety sensitivity (Paulus & Stein, 2006), suggesting altered signal may be present in this highly anxious sample. Perhaps then heightened activity in this area across trial types and threat context is symptomatic of this potential neuroanatomical marker of anxiety sensitivity. Indeed, heightened BOLD response in the insular cortex in simple phobia, obsessive-compulsive disorder and post-traumatic stress has been documented (Paulus & Stein, 2006; Rauch, Savage, Alpert, Fischman, & Jenike, 1997), though full discussion of this in the context of the present study would require a healthy control comparison. The insular cortex was also consistently identified in chapter 4, in both simple avoidance and goal-conflict trials, suggesting the JORT does access defensive behaviour to some degree. However, as shown in chapter 4 this was in the context of other, more differential, neural activations in simple avoidance relative to goal-conflict. Absence of differential neural activation across purportedly different types of trial suggests that there is instead a great deal of similarity between these trial types in the JORT.

Considered in combination with the criticisms of the goal-conflict arm of the JORT, perhaps the lack of differential neural activation between trial types indicates that the current arms of the JORT task are best understood as two variants of active avoidance, with one requiring more motor complexity than the other. This opens the door to improvements to the JORT paradigm, including introduction of an approach-reward aspect and increased choice for participant response to threat. Potential additions to the JORT paradigm are outlined in the discussion chapter of this thesis.

Right supplementary motor cortex, right supramarginal gyrus, right superior parietal lobule and left inferior occipital gyrus activity correlated with oscillations during flight. The parietal lobe has been associated with allocation of attention (Shuhama et al., 2017) suggesting heightened concentration as more complex movements are made. Parietal cortical activity has also been associated with exploration of environment (Loh et al., 2017), which is logically connected to oscillatory movements. Activation of the supramarginal gyrus is also suggestive of greater movement complexity, with lesions here associated with apraxia in stroke patients (Dreßing et al., 2015). Meanwhile, the supplementary motor area has been linked to successful and unsuccessful action monitoring (Chem, Etcheberrigaray, Ito, Kim, & Alkont, 1994) indicating oscillations may play an exploratory role; this potentially supports the

use of oscillation measurements in observation of risk assessment type behaviours, which in rodents serve the purpose of threat exploration (Perkins et al., 2009). However, as mentioned above, inclusion of actual additional information gain from cautious approach might improve accuracy of compatibility with rodent models.

5.6.1 Strengths & limitations

The use of two anxiolytics with different mechanisms of action in this protocol is a strength, ensuring results are not limited to one neurochemical system. Further, exploration of effects in an anxious sample and high neuroticism is an important addition to the field. The number of participants included in the analysis was in line with required sample size, as defined by power calculations.

However, there are key limitations to the current paradigm. A technical fault meant that cardiac and respiratory data were not recorded during task completion; this meant that these biological factors could not be controlled for in the imaging analysis as is often done when assessing BOLD response. Collection of this data would have had the added benefit of providing a biological marker of anxiety throughout the experiment for comparison with the neural data. This would have been interesting considering the lack of neurological and behavioural difference in threat vs. non-threat trials and might have provided more insight on the suggestion that anxiety levels were high throughout the paradigm. Due to excessive motion, the number of participants included in some conditions was reduced. Though still within the bounds of acceptable power when identifying large effects, the exclusion of multiple individuals may be problematic for identification of more moderate effects. Participants were selected on the basis of neuroticism scores one standard deviation above population average, as this is an acknowledged risk factor for anxiety disorders (Lahey, 2009). It is not possible to say that findings are generalizable outside this selection standard, so further work outside this category is important. Inclusion of a healthy control comparison group would have also been advantageous.

5.7 Conclusion

This study aimed to explore the neural predictions of RST and the findings of chapter 4, using two anxiolytics and a human translation of the MDTB in a sample of individuals with high neuroticism and

GAD. The key predictions of RST were not observed in this first exploration in anxious individuals; further, aside from activation of the anterior insula during response to threat, the findings of chapter 4 were not replicated. Though unlikely, it is not possible to say whether this is reflective of true differential neural activation in anxiety relative to healthy controls (as chapter 4 involved exclusively healthy controls), or whether more probably the findings indicate fundamental paradigm design issues. As such, it is not possible to draw strong conclusions about threat avoidance and goal-conflict related neural activity in highly neurotic individuals with GAD, nor the effect of benzodiazepine and cholinergic-modulators on this. The study did however indicate the importance of the anterior insula in threat and anxiety, in support of chapter 4. Further, results outlined a differential anxiolytic response dependent on individual differences in threat magnification as measured by the FSS, which has important implications for treatment, as lower-end FSS scorers were shown to have greater reactivity to fear after benzodiazepine administration. This finding is also pertinent to a multi-level approach to transdiagnostic mechanisms in GAD, indicating the importance of looking beyond neuroticism in isolation.

Chapter 6: Self-reflection in mood & anxiety disorders: neuroticism, self-criticism and perception of performance.

6.1 Chapter summary

As the specificity of neuroticism across anxiety and depression is poor (Kotov et al., 2010; Lahey, 2009), exploration of individual differences within broad domain-level traits could enhance understanding of psychological processes and co-morbidities (Caspi & Moffitt, 2018; Claridge & Davis, 2001) and aid a multi-level approach to transdiagnostic factors. Forms of negative self-reflection such as self-criticism and negative self-judgment have been linked to both neuroticism and mood and anxiety disorders (Cox et al., 2004; Coyne & Whiffen, 1995; Iancu et al., 2015) and as such may be of interest in expanding our understanding of broad mechanistic processes in psychopathology. This chapter aimed to explore aspects of negative self-reflection in association with neuroticism in select mood and anxiety disorders. An additional aim was to pilot the Fake IQ Test (FIQT), a novel adaptation of a measure of perception of (own) performance first designed by Nuttin & Greenwald (1968), in an adult psychiatric population. Online questionnaires and behavioural tasks were administered to 784 adult participants, who reported any lifetime diagnoses of Major Depressive Disorder (MDD) and/or Generalized Anxiety Disorder (GAD).

Analysis revealed significantly higher neuroticism, self-criticism and negative performance perceptions in all the diagnostic groups relative to healthy controls. Modelling of the relationship between neuroticism, performance perception and self-criticism indicated a key role for neuroticism in self-critical attitude, which varied slightly across disorders; further, agreeableness and conscientiousness were shown to have a slight negative effect on the relationship between neuroticism and self-criticism, whilst extraversion played a small positive role. Comparison of groups indicated significantly lower ability to self-reassure in MDD vs. GAD. Self-hatred differentiated singular MDD or GAD diagnoses from individuals with a history of both. The results have potential implications for assessing risk and treatment paradigms. Self-criticism, agreeableness, conscientiousness and extraversion all had relevant relationships with MDD, GAD and co-morbidity, and are easily captured with non-invasive self-report

measures. More specifically, the ability for measures such as self-reassurance and self-hatred to highlight specific ‘weak spots’ in certain disorders could impact treatment choice. Finally, the FIQT pilot indicated differential relationships between perceptions of performance and self-criticism in health and pathology, the implications of which are discussed.

This chapter reflects part of a manuscript currently in preparation for submission to the journal of Psychological Medicine, of which I am joint first author.

6.2 Introduction

Neuroticism is a domain-level trait measuring emotional stability (Costa & McCrae, 1992) and is a robust risk factor for affective disorders (Kendler et al., 2004; Neeleman et al., 2001), such as Major Depressive Disorder (MDD) (Bagby & Rector, 1998) and Generalized Anxiety Disorder (GAD) (Kotov et al., 2010; Lahey, 2009), and co-morbidity between these disorders (Takahashi, Roberts, Yamagata, & Kijima, 2015; Moffitt et al., 2007). Though questionnaire measures of neuroticism are a promising tool for identification of those at risk of anxiety disorders due to straightforward self-report format and low emotional-impact questions (Patrick et al., 2018), its specificity is poor (Claridge & Davis, 2001; Lahey, 2009).

Consideration of individual differences within domain-level traits can advance understanding of associated psychological and pathological processes (Cox et al., 2001; Paunonen, 1998); explaining the role of neuroticism in expression of lower-level individual differences and how variation in this relates to pathology could improve precision identification, and potentially impact treatment of disorders (Claridge & Davis, 2001; Lahey, 2009). Self-criticism is a candidate of interest as it sits within the broader domain of neuroticism (Cox et al., 2004; Coyne & Whiffen, 1995) and is highly associated with both psychopathology (Hermanto et al., 2016; Kopala-Sibley et al., 2015) and poor psychotherapeutic outcomes (Blatt, 1995; Egan, Wade, & Shafran, 2011). For example, despite a therapeutic focus on social dysfunction rather than enduring personality traits (Feijo De Mello, De Jesus Mari, Bacaltchuk, Verdeli, & Neugebauer, 2005), self-criticism has been shown to predict poorer outcomes in interpersonal therapy (Marshall, Zuroff, McBride, & Bagby, 2008). Further, the level of reduction in

self-criticism during treatment is a significant predictor of treatment outcome in MDD and social anxiety disorder (SAD) (Blatt, 1995; Rector et al., 2000). Models of self-criticism in pathology have highlighted comparative self-criticism (negative opinion of self in relation to others) and inability to feel self-satisfaction as core self-critical aspects leading to psychological distress (Besser, Flett, & Hewitt, 2004; Hermanto et al., 2016; Misslidine, 1963; Thompson & Zuroff, 2004).

Conversely, pro-social traits (Hjemdal, 2007; Yuan et al., 2011) and related personality dimensions such as extraversion and conscientiousness (Campbell-Sills, Cohan, et al., 2006) may be protective in psychopathology. Agreeableness has been shown to moderate the relationship between neuroticism and negative outcomes (Ode & Robinson, 2007), reducing adverse experiences. This interaction has not been explored with extraversion and conscientiousness, despite their prosocial aspects (Carlo, Okun, Knight, & de Guzman, 2005) and thus protective potential. Further, (low) extraversion is considered psychopathological whilst (high) conscientiousness and agreeableness are thought conducive to treatment adherence and success (Marshall et al., 2008). As aforementioned, self-criticism is a negative outcome associated with neuroticism (Clara, Cox, & Enns, 2003) and has also been linked to increased risk for dangerous behaviours within mental health such as self-harm (Gilbert et al., 2010). As such, understanding the potential protective facets of stable and easily measurable broad-domain traits such as agreeableness, extraversion and conscientiousness in the relationship between neuroticism and negative outcomes could aid identification of particularly vulnerable populations.

Negative self-judgment of ability is a further factor that may provide additional insight. Exploration of personality and concepts related to self-judgement, such as confidence, have shown extraversion and openness to be predictors of overconfidence (Schaefer et al., 2004). However, the role of neuroticism is less definite. Lower levels of neuroticism are associated with self-confidence in the literature (Cheng & Furnham, 2002), whilst other researchers have not found evidence to link neuroticism with areas of specific confidence, such as belief in academic ability (Pulford & Sohal, 2006). Neuroticism involves a tendency towards negative emotionality, poor response to stress and perception of neutral situations as threatening (McCrae & Costa, 1987; Widiger, 2009); neuroticism may thus result in heightened negative interpretation of events and performance, even when the situation is neutral. Several theories

have suggested a basis for the relationship between confidence and mental health diagnoses such as depression. For example, Beck and colleagues outlined systematic negative distortion of information as central to depressed individuals (Beck, Rush, Shaw, & Emery, 1979), by necessity colouring the individual's perception of their own ability and performance. Contrastingly, other theorists suggest individuals experiencing depression may interpret their own ability more realistically than psychiatrically healthy people (Szu-Ting Fu, Koutstaal, Poon, & Cleare, 2012). Given the overlap of negative emotionality and distorted perception associated with both neuroticism and depression (DeMonbreun & Craighead, 1977; McCrae & Costa, 1987; Widiger, 1992), a relationship between neuroticism and perception of own ability appears plausible.

Though overconfidence is common in the general population (Bhandari & Deaves, 2006; Bruin & Kok, 2017; Schaefer et al., 2004), the relationship between overconfidence and mental health is less clear. This is exemplified in contradicting evidence linking depression to both over estimation of performance accuracy (Dunning & Story, 2001) and under confidence in retrospective judgement (Szu-Ting Fu et al., 2012). Greater expectations of failure and negative self-judgement is associated with MDD (Fu et al., 2005; Szu-Ting Fu et al., 2012; Wener & Rehm, 1975), whilst perfectionist attitude is linked to anxiety (Besser et al., 2004). Self-judgement in mood and anxiety disorders has been divided further; a general negative self-perception across situations has been highlighted in depression (Gilbert, Clarke, Hempel, Miles, & Irons, 2004), whereas a more specific negative comparison of self to others features is identified in anxiety (Werner et al., 2012). Though not unanimous (e.g. DeMonbreun & Craighead, 1977; Nelson & Craighead, 1977) these findings suggest potential for discrimination based on perception of (own) performance. As with self-criticism, negative self-reflection and high levels of perfectionism have been linked to poor treatment outcomes in anxiety and depressive disorders (Egan et al., 2011). The link between perception of performance and self-criticism has not fully been explored, with a particular paucity of research in anxiety diagnoses outside of social anxiety disorder.

Self-judgement is commonly measured via questionnaires involving global reflection on past experience (for example, the Rosenberg Self-Esteem Scale; Rosenberg, 1979) or with academic tasks employing feedback (Fu et al., 2005; Nelson & Craighead, 1977). However, feedback can have an

artificial effect on self-judgement (Besser et al., 2004) and academic focus might be influenced by prior experience and expectations. Further, there is some suggestion that measures with a reliance on semantic autobiographical memory may be insensitive to change in populations with lower levels of insight (Offer et al., 2000; Orfei et al., 2008). Here, we adapted a tool designed to measure perceptions of success and failure in adolescents (Nuttin & Greenwald, 1968) with the aim of avoiding these potential confounds.

6.2.1 Development of the Fake IQ Test

6.2.1.1 Nuttin & Greenwald's (1968) original measure

In the original experiments, participants were shown visual stimuli or mathematical equation pairs and asked to choose which of the pair was (e.g.) larger. Though the stimuli had slight visual differences, the quality on which participants were asked to judge them (e.g. size) was identical in both stimuli making the correctness of their response indiscernible. Participants received correct/incorrect feedback from the experimenter according to a prearranged schedule, rather than dependent on performance. After completing the series, participants were asked: 1) how many times they thought they were correct and incorrect; and 2) if they were satisfied with their performance. The findings from the original series of experiments indicated that individuals perceive successes and failures in the context of a pre-established self-conception (Nuttin & Greenwald, 1968).

6.2.1.2 The FIQT adaptation

The Fake IQ Test (FIQT) was explained to participants as a measure of visual perception ability and as in the original, required participants to identify supposed differences between two stimuli that are in fact identical. In contrast to typical approaches, no accuracy feedback was provided or assessed (as the items were identical and thus individuals could not be 'correct'). In addition to removing feedback to prevent mood and judgement alterations during the task (Besser et al., 2004) and removing academic skill elements from the task, we altered questions asked to tap peer-self comparison (peer-comparison) and self-satisfaction specifically. The reason for this was two-fold: 1) to explore the utility of this measure in a psychiatrically relevant adult population, as it has previously only been used in adolescents

(Nuttin & Greenwald, 1968) who have less stable personality constructs (Roberts & DelVecchio, 2000); and 2) to assess individual perceptions of performance in self-critical attitudes and pathology in the absence of feedback in order to demonstrate individual perception without experimenter manipulation. Critiques of self-criticism measures suggested that global self-reflective tasks create potential for self-bias (Iancu et al., 2015). In addition to the core aims, if the FIQT measures behaviour parallel to self-criticism it might be an alternative measure for use in neuroimaging in particular, as the validity of using imagined states in this context has been brought in to question (Klein & Gangi, 2010; Prigatano & Fordyce, 1986). Given the association between negative self-judgement and therapeutic outcomes (Blatt, 1995; Rector et al., 2000) development of a tool that can tap perception of ability without the potential mood confounds presented by feedback and academic focus would be of interest. The FIQT also has little reliance on imagined state or requirement for high levels of vocabulary, which would mean this tool could have applicability in, for example, paediatric research.

6.2.2 Hypotheses & aims

Neuroticism, self-criticism and perceptions of performance are expected to be significantly elevated in groups with self-reported MDD, GAD or dual experience of both (as no information regarding chronology of diagnoses was collected, temporal co-morbidity cannot be confirmed in the present sample) in their lifetime, relative to those reporting no previous mental health diagnosis (healthy controls, HC). The dual grouping is predicted to have higher neuroticism, self-criticism and negative perception of performance than MDD and GAD groups due to potentially greater disease burden and links between neuroticism and co-morbidity (Lahey, 2009). Neuroticism is expected to show positive correlations with self-criticism, suggesting higher neuroticism levels are associated with greater self-criticism. Though the literature is currently not clear, perception of performance (peer-comparison and self-satisfaction) scores are expected to show a negative relationship with neuroticism and self-criticism, indicating higher ratings of satisfaction and favourable comparison with peers is associated with lower levels of neuroticism and self-criticism.

It is also predicted that FIQT and self-criticism scores will correlate (regardless of group), indicating the FIQT is a tool able to tap negative self-judgement without reliance on imagined state and in the absence of potentially mood-altering confounds, such as feedback.

Structural equation modelling of neuroticism and perception of performance as indicator variables in self-criticism in HC and diagnostic groups was expected to show strong roles for both indicator variables. As negative perceptions of the self are characteristic of depression (Gilbert, Clarke, Hempel, Miles, & Irons, 2004) self-satisfaction in perceptions of performance is expected to be raised in the MDD sample. Conversely, self-criticism arising from negative peer-comparison is predicted to be particularly elevated in GAD in line with previous work (Werner et al., 2012).

6.3 Method

6.3.1 Participants

Participants were recruited from the general population via online platforms (Gumtree, Facebook), and through university email circulars, with no enrolment restrictions. Further information can be found in chapter 2.

6.3.2 Materials

6.3.2.1 The Trait Self-Description Inventory

The Trait Self-Description Inventory (TSDI Collis & Elshaw, 1998) is a 50-item version of the TSDI was adapted for online use. The TSDI is a self-report questionnaire measuring the Big-5 personality traits of openness (to experience), conscientiousness, extraversion, agreeableness and neuroticism.

6.3.2.2 The Forms of Self-Criticising/Attacking and Self-Reassuring Scale

The Forms of Self-Criticising/Attacking and Self-Reassuring Scale (FSCSRS; Gilbert et al., 2004) is a well-validated 22-item self-report scale, exploring tendency to be self-critical or self-reassuring in personal setbacks and failures. The FSCSRS includes subscales measuring perceptions of own inadequacy (inadequate-self), hatred towards self (hatred-self) and ability to self-reassure (reassure-self). Reliability scores for the subscales are good (inadequate-self, .94; hatred-self, .90; reassure-self,

.87) (Baião, Gilbert, McEwan, & Carvalho, 2015). Answers are provided on a 4-point Likert scale, responding to questions such as “I am easily disappointed with myself” (inadequate-self), “I have a sense of disgust with myself” (hatred-self) and “I find it easy to like myself” (reassure-self). The inadequate-self and hated-self subscales can be totalled to give an overall self-criticism score (Baião et al, 2015).

6.3.2.3 The Fake IQ Test (FIQT)

A measure of performance perception adapted from Nuttin & Greenwald (1968; see above), the Fake IQ Test (FIQT) was presented to participants as a measure of visual perception. Participants were required to make comparative judgements about a parameter of a pair of complex visual stimuli (i.e. which cluster of dots contains the most dots, which shape has the larger surface area, or which line is longer) displayed side-by-side on screen. The two shapes are equivalent on the parameter of interest, though appear to have measurable differences, and thus there is no correct answer. Participants were not given any feedback on their performance. Participants were asked to rate their satisfaction with their performance (self-satisfaction) and how well they believe they have performed relative to peers completing the same task (peer-comparison) after every block of 5 image pairings, completing 9 blocks in total (45 image pairings). Answers are given on a 4-point Likert scale (for satisfaction and peer comparison respectively: not at all satisfied, not very satisfied, a bit satisfied, completely satisfied; very much worse, a bit worse, a bit better, very much better). Peer-comparison and self-satisfaction composite scores are calculated by totalling the answers to each of these questions provided by participants at the end of each block (i.e. a sum of 9 answers for each total score).

At the end, participants were asked to rate how important their performance on the task was using a visual analogue scale (VAS) from 0-100. See Figure 14 for example FIQT stimuli pairings. Participants only saw the acronym for this measure and were unaware of its full title.

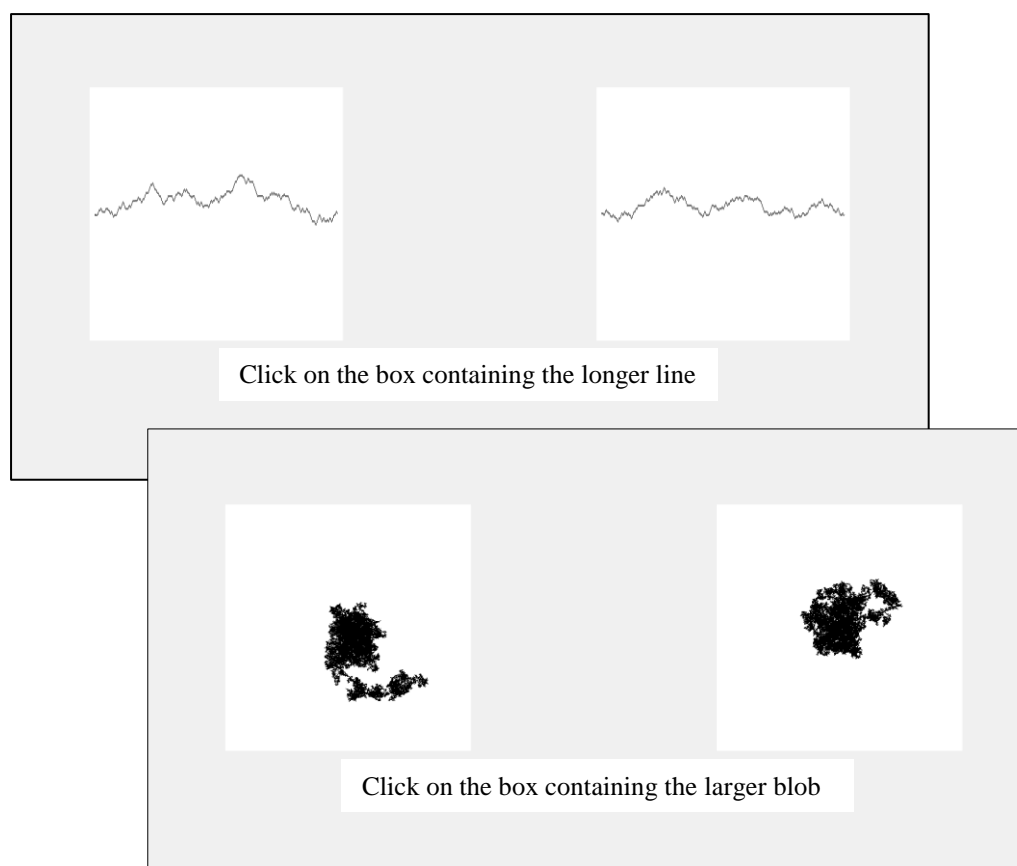


Figure 14 Example stimuli pairings from the Fake IQ Test (FIQT)

6.3.3 Design

All data were collected online via a specially designed platform (www.measureyourpersonality.com). Candidates saw the information sheet and online consent form, before completing a series of brief questions (including age, gender and whether they had ever been diagnosed with mental health conditions). Following, participants completed in order the TSDI, the FIQT and the FSCSRS in order before being debriefed.

6.3.4 Statistical analysis

Data were analysed using SPSS and AMOS Versions 23.0 (SPSS Inc. Chicago, US). Basic relationships between perceptions of performance (FIQT), personality (TSDI) and self-criticism (FSCSRS) were explored with bivariate correlations. Between group (HC, MDD, GAD, dual) differences were explored

with ANOVA and post-hoc t-tests. A formative structural equation model (SEM) regressing personality (neuroticism, TSDI) and perceptions of performance (FIQT) against self-critical self-concept (FSCSRS) was created in AMOS. SEM cannot inform causality as our data is cross-sectional but is used here to indicate diagnosis-specific differences in self-criticism variance attributable to personality and performance perception. Model fit was evaluated using chi-squared, goodness-of-fit index (GFI), Comparative Fit Index (CFI) and Root Mean Square Error of Approximate (RMSEA) where appropriate.

6.3.4.1 Power calculations

Power calculations using G*Power suggest a sample size of at least 42 for comparison of means and correlational or regression analysis with 4 groups with a large expected effect size ($1-\beta = .95$, $\alpha = .05$, $d = .80$). A sample size of 111 is suggested for a more moderate effect size ($1-\beta = .95$, $\alpha = .05$, $d = .30$) (Faul et al., 2009, 2007). This information informs group comparison statistics (exploring differences in measures between healthy and diagnosed groups), correlations between measures and planned structural equation modelling outlined in section 6.2.2.

6.4 Results

A total of 871 participants aged 18 to 82 ($M = 26.15$, $SD = 8.42$) completed the study. Participants self-reporting a diagnosis of MDD ($n = 91$), GAD ($n = 27$), dual MDD and GAD ($n = 53$) and those reporting no previous mental health diagnosis (healthy controls, HC; $n = 577$), were included in analysis. Additional co-morbidities were permitted (substance abuse, eating disorders) across groups excluding the healthy controls; co-morbid anxiety of any type (specific phobia, social anxiety) was not permitted in the MDD group but was allowed in the GAD and dual groups. Demographic and key variable averages are in Table 15, below.

Table 15

Average (mean) demographic and key variable scores

	Total	HC	MDD	GAD	Dual
	N (% female)				
Gender	784 (77.0)	577 (75.6)	91 (82.4)	27 (88.9)	53 (77.4)
	Mean (SD)				
Age	26.0 (8.5)	25.4 (8.1)	31.1 (11.1)	24.6 (3.9)	25.0 (6.6)
Openness	45.7 (12.1)	44.7 (12.2)	49.4 (10.8)	46.8 (12.2)	49.2 (10.7)
Conscientiousness	50.2 (10.7)	51.0 (10.3)	47.6 (10.7)	50.6 (14.1)	46.1 (12.0)
Extraversion	-3.98 (14.2)	-3.99 (14.4)	-3.8 (12.7)	1.15 (13.5)	-6.9 (14.3)
Agreeableness	47.0 (10.1)	46.7 (10.0)	47.3 (10.5)	52.0 (8.6)	46.8 (10.3)
Neuroticism	48.8 (15.7)	46.7 (15.5)	53.4 (14.8)	57.0 (14.7)	59.0 (12.1)
FIQT-Peer	23.5 (4.2)	23.8 (4.0)	22.5 (4.2)	22.8 (3.9)	21.2 (4.9)
FIQT-Satisfied	24.9 (4.8)	25.1 (4.7)	24.5 (4.7)	24.3 (4.8)	23.6 (5.7)
FIQT Important	50.0 (26.4)	49.3 (26.5)	48.2 (26.4)	61.7 (25.0)	54.0 (25.1)
FSCSRS Hatred	3.9 (4.3)	3.3 (3.7)	5.7 (5.0)	4.3 (4.8)	7.9 (6.3)
FSCSRS Inadequate	20.1 (8.1)	19.0 (7.9)	23.0 (7.7)	24.0 (7.8)	25.1 (8.2)
FSCSRS Reassure	19.3 (6.6)	20.4 (6.1)	15.4 (7.1)	18.5 (6.4)	15.3 (7.4)
FSCSRS Total	24.0 (11.4)	22.2 (10.6)	28.7 (11.8)	28.3 (11.6)	33.0 (13.2)

M, mean; SD, standard deviation; HC, healthy control; MDD, major depressive disorder; GAD, generalized anxiety disorder; FIQT-Peer, Fake IQ Test peer-comparison; FIQT-Satisfied, Fake IQ Test self-satisfaction; FSCSRS, Forms of Self-Criticising and Self-Reassuring Scale (self-hatred, self-inadequacy and self-reassuring sub-scales)

Bivariate correlations show significant associations between all key variables when the sample was combined (all $<.001$). Observed correlations are presented in Table 15, broken down by group (HC, MDD, GAD and dual).

Table 16

HC, MDD, GAD and dual group correlations between neuroticism, perception of performance and self-criticism scores (HC top right corner)

		1	2	3	4	5	6	7
1. Neuroticism	MDD	-	-.119**	-.040	.447**	.669**	.656**	-.488**
	GAD	-						
	Dual	-						
2. FIQT-Peer	MDD	-.201	-	.653**	-.185**	-.246**	-.248**	.350**
	GAD	-.518**	-					
	Dual	-.067	-					
3. FIQT-Satisfied	MDD	-.193	.743**	-	-.132**	-.131**	-.144**	.198**
	GAD	-.301	.797**	-				
	Dual	-.018	.609**	-				
4. FSCSRS Hatred	MDD	.594**	-.255**	-.211**	-	.617**	.808**	-.536**
	GAD	.621**	-.359	-.207	-			
	Dual	.647**	-.101	-.008	-			
5.FSCSRS Inadequate	MDD	.650**	-.188	-.181	.702**	-	.962**	-.588**
	GAD	.515**	-.344	-.244	.668**	-		
	Dual	.647**	-.063	.037	.650**	-		
6. FSCSRS Reassure	MDD	-.670**	.242*	.151	-.649**	-.667**	-	-.626**
	GAD	-.542**	.462*	.282	-.640**	-.459*	-	
	Dual	-.486**	.491**	.230	-.514**	-.539**	-	
7. FSCSRS Total	MDD	.678**	.242**	-.208*	.885**	.952**	-.713**	-
	GAD	.605**	-.374	-.250	.864**	.952**	-.574**	-
	Dual	.681**	-.087	.019	.882**	.931**	-.580**	-

HC, healthy control; MDD, major depressive disorder; GAD, generalized anxiety disorder; Dual, dual GAD & MDD; FIQT, Fake IQ Test (peer-comparison and self-satisfaction sub-scales); FSCSRS, Forms of Self-Criticising and Self-Reassuring Scale (self-hatred, self-inadequacy and self-reassure sub-scales)

* $p < .05$

** $p < .001$

As expected, neuroticism significantly correlated with self-criticism (FSCSRS subscales) and perceptions of performance (FIQT subscales). The FSCSRS self-reassure scale had a divergent relationship between healthy controls compared to the MDD, GAD and dual groups: a positive relationship between neuroticism and ability to reassure self was shown in the former, but a negative relationship in the latter. FIQT-peer correlated with neuroticism only in the HC and GAD subsamples. FIQT-peer and FIQT-satisfied showed robust correlations with self-criticism in the HC group. Correlations between FIQT subscales and self-criticism were mixed in the diagnostic groups.

Differences in neuroticism, FSCSRS and FIQT between groups was assessed with a one-way ANOVA. Significant differences across the FSCSRS and in FIQT-Peer were shown, though the importance of performing well on the FIQT ($p = .062$) and FIQT-Satisfied ($p = .103$) did not reach significance. Due to large differences in sample size across the groups, 27 cases from the HC, MDD and dual groups were selected for comparison with the GAD population, and the ANOVA re-run as a test of sensitivity. Findings were largely replicated in this second analysis, though differences in openness and agreeableness became non-significant. See Table 17 for details.

Table 17

Comparison of self-reported neuroticism, perception of performance and self-criticism scores between groups (HC, MDD, GAD and dual)

	Full sample ¹		Sensitivity replication ²	
	f	p	f	p
Neuroticism	16.826	<.001**	5.564	.001**
Openness	5.841	.001**	2.205	.092
Conscientiousness	5.391	.001**	1.329	.269
Extraversion	1.903	.128	2.615	.055
Agreeableness	2.404	.066	1.961	.124
FIQT-Peer	9.165	<.001**	6.732	<.001**
FIQT-Satisfied	2.066	.103	1.964	.124
FIQT-Important	2.430	.064	2.007	.118
FSCSRS Hatred self	27.300	<.001**	9.290	<.001**
FSCSRS Inadequate self	17.547	<.001**	8.696	<.001**
FSCSRS Reassure self	24.110	<.001**	8.910	<.001**
FSCSRS Total	24.219	<.001**	9.562	<.001**

ANOVA, analysis of variance; HC, healthy controls; MDD, major depressive disorder; GAD, generalized anxiety disorder; Dual, dual GAD & MDD; FIQT, Fake IQ Test; FSCSRS, Forms of Self-Criticising and Self-Reassuring Scale

** Significant at $p < .001$

¹ HC (n = 577); MDD (n = 91); GAD (n = 27); dual (n = 53)

² HC (n = 27); MDD (n = 27); GAD (n = 27); dual (n = 27)

Individual samples T-tests were conducted to assess between-group differences, with findings generally indicating higher ratings of self-criticism and neuroticism in diagnosed groups. Comparison of the diagnostic groups (MDD, GAD and dual) revealed a significant difference in FSCSRS reassure score

between MDD and GAD (showing lower self-reassurance in MDD), and significant differences in neuroticism, FSCSRS hatred and FSCSRS total scores between the MDD and dual samples. When comparing GAD and dual groupings, only the FSCSRS hatred finding remained significant. Full results are shown in Table 18, below.

Table 18

Between-group comparison of neuroticism perception of performance and self-criticism

	MDD (n = 91)			GAD (n = 27)		Dual (n = 53)
	<i>t</i>			<i>t</i>		<i>t</i>
	HC	GAD	Dual	HC	Dual	HC
Neuroticism	-3.852	-1.093	-2.284*	-3.360**	-.630	-5.560**
FIQT-Peer	2.959*	-.341	1.738	1.315	1.523	4.574**
FIQT-Satisfied	1.112	.271	1.060	.938	.507	2.215*
FSCSRS Hatred self	-5.595**	1.245	-2.311*	-1.487	-2.588*	-8.233**
FSCSRS Inadequate self	-4.568	-.590	-1.553	-3.253**	-.584	-5.428**
FSCSRS Reassure self	7.027*	-2.027*	.115	1.555	1.925	5.702**
FSCSRS Total	-5.372	.139	-2.032*	-2.943**	-1.565	-6.989**

MDD, major depressive disorder; GAD, generalized anxiety disorder; FIQT, Fake IQ Test (subscales peer-comparison and self-satisfaction); FSCSRS, Forms of Self-Criticising and Self-Reassuring Scale (subscale self=hatred, self-inadequacy, self-reassurance and total).

* $p < .05$

** $p < .005$

Agreeableness, extraversion and conscientiousness were explored as moderators of the relationship between neuroticism and self-critical output using hierarchical regressions within each of the groups (HC, MDD, GAD and dual). Agreeableness and neuroticism accounted for a significant amount of variance in self-criticism in the GAD group ($R^2 = .379$, $f(2, 24) = 7.337$, $p < .005$). These factors were then centred to provide an interaction term and to limit multicollinearity (Aiken, West, & Reno, 1991) indicating the interaction accounts for a significant but small amount of variation (R^2 change = .017, $f(3, 23) = 5.037$, $p < .05$). This process was repeated, indicating moderation of the neuroticism- self-criticism relationship by agreeableness also in the dual group ($R^2 = .686$, $f(3, 49) = 22.173$, $p < .001$; $R^2 \Delta = .012$, $f(3, 49) = 15.203$, $p < .001$). Extraversion ($R^2 = .683$, $f(2, 50) = 21.813$, $p < .001$; $R^2 \Delta = .010$, $f(3, 49) = 14.818$, $p < .001$) and conscientiousness, ($R^2 = .681$, $f(2, 50) = 21.592$, $p < .001$; $R^2 \Delta = .012$, $f(3, 49) = 14.789$, $p < .001$) only moderated the relationship between neuroticism and self-criticism in the dual group.

Plotting these interactions revealed that extraversion had a small positive effect (increased extraversion slightly reduced the interaction between neuroticism and self-criticism) in the dual group, and that agreeableness and conscientiousness both had very small negative effects (slightly increasing the relationship between neuroticism and self-criticism). However, these effects were small (Cohen, 1988) and at most only explained 1.7% additional variance.

6.5 Discussion

This study explored the role of individual differences in neuroticism, perception of own performance and self-critical attitude in differentiation between affective disorders. As predicted, significant differences in neuroticism, self-criticism and peer-comparison were observed between healthy controls and those with diagnoses, in line with the literature (Cox et al., 2000; Fu et al., 2005; Iancu et al., 2015; Wener & Rehm, 1975) and the clinical profiles of these disorders (American Psychiatric Association, 2013a). Comparison of the diagnostic groups indicated significantly higher self-reassurance in GAD relative to MDD. Contra to hypothesis, differentiation of MDD and GAD based on peer-comparison or self-satisfaction was not possible. Dual diagnosis was associated with greater self-hatred than either

MDD or GAD alone and was also shown to related to higher overall self-criticism and neuroticism than the MDD group.

Self-hatred scores were significantly higher in the dual group relative to both GAD and MDD, and there was significantly greater ability to self-reassure in the GAD group compared to MDD. Self-hatred has been identified as a prominent block in self-compassionate therapeutic approaches (Gilbert & Procter, 2006) whilst ability to self-reassure has been shown to attenuate negative reactions in a manner more beneficial than self-esteem (Leary, Tate, Adams, Allen, & Hancock, 2007). Neuroticism was shown to have a differential relationship with the ability to self-reassure in healthy compared to unhealthy groups, such that in the former higher neuroticism was related to better self-reassurance, and in the latter was related to worse self-reassurance. This finding is unexpected, given the almost exclusive association between neuroticism and negative outcomes in the literature (Lahey, 2009); ‘healthy’ neuroticism has been hinted at in the physical health literature (Friedman, 2000) and as such, a ‘helpful’ degree of neuroticism may also be present in mental health. Self-hatred and self-reassurance (self-compassion) are core components of therapeutic approaches such as Compassionate Mind Training (CMT; Gilbert, 2000; Gilbert & Procter, 2006). These findings highlight how relevant individual variations in these factors could be. Therapies such as CMT may be more appropriate to samples with particularly poor self-reassurance and high levels of self-hatred, such as those with MDD or multiple diagnoses within mood and anxiety disorders, allowing for more targeted intervention.

As neuroticism scores of more than one standard deviation above the population average are considered risk factors for psychopathology (Lahey, 2009) broad level screening for psychiatric risk is possible (Patrick et al., 2018). However, if neuroticism is considered trans-diagnostic and magnitude of scores is not necessarily distinct between disorders, awareness of the disorder-specific variation has ramifications for identification of risk. Analysis indicated differential moderation of the relationship between neuroticism and self-criticism between diagnostic groups via co-existing personality traits. Agreeableness, conscientiousness and extraversion have been linked to higher self-compassion (Neff, Rude, & Kirkpatrick, 2007) and are thought to be protective in psychopathology (Campbell-Sills, Cohan, et al., 2006) though here had a slightly negative effect instead; potentially, at least for

conscientiousness, this may reflect associations between this trait and perfectionism (Stoeber, Otto, & Dalbert, 2009), though effect sizes were very small. Extraversion did have a small positive effect in reducing the relationship between neuroticism and self-criticism. Though the self-criticism questionnaire does not explicitly explore self-confidence, the findings presented here are largely in line with evidence that extraversion and other prosocial traits such as agreeableness are associated with greater confidence (for example, Schaefer et al., 2004).

If different prosocial traits have distinct resilience-type roles between diagnoses, these traits could be exploited to promote diagnosis-specific resilience against self-critical attitudes in those with raised neuroticism or as additional identifiers of those at risk increased negative symptoms (such as high levels of self-criticism). This is especially pertinent given the relationship between self-criticism (Gilbert et al., 2010) or specifically self-dislike (Claes, Nederkoorn, Vandereycken, Guerrieri, & Vertommen, 2006) and self-harm, especially within mood and anxiety disorders (Haw, Hawton, Houston, Townsend, & Ton, 2012). Individuals with MDD or dual diagnosis who are low in self-reassurance and have specific profiles of pro-social traits may represent a highly vulnerable group. High neuroticism and/or low agreeableness in depression is associated with better response to pharmacotherapy rather than cognitive-behavioural therapy, due to innate characteristics of these personality traits (Bagby et al., 2008), suggesting that awareness of broad-domain traits can inform treatment decision and lead to improved tailored care packages. These findings highlight the importance of thinking beyond neuroticism and supports some traits as having disorder-specific implications (Coyne & Whiffen, 1995; Zuroff, Mongrain, & Santor, 2004). Age of onset, disease duration and chronicity might be interesting to consider here also. Given the easy self-report nature of these measures, awareness of such factors as neuroticism, prosocial traits and self-critical attitudes could be a cost-effective and accessible means of improving this aspect of medical care.

This initial exploration of the FIQT indicated raised negative attitude to the self in comparison with others (peer-comparison) in those diagnosed with GAD, MDD or dual diagnosis as predicted in line with evidence (Cox et al., 2000; Iancu et al., 2015). Neuroticism was shown to negatively correlate with peer-comparison in GAD and healthy controls; this partially supports the literature, which indicates low

levels of neuroticism are associated with greater self-confidence (Cheng & Furnham, 2002). Curiously, peer-comparison and self-satisfaction only correlated with total self-criticism in healthy controls and MDD. Contra to hypothesis, self-satisfaction within the FIQT did not significantly differ between HC and diagnostic groupings. This is unexpected, as the inability to feel self-satisfaction has been posited as a differentiator of healthy and unhealthy cognition (Besser et al., 2004; Missludine, 1963). Similarly, there was no evidence to support worse self-satisfaction in MDD and peer-comparison in GAD, contrary to predictions made from the literature (Gilbert et al., 2004; Werner et al., 2012). Ego-involvement may be integral to the relationship between perfectionist self-critical attitudes and anxiety (Flett, Hewitt, Blankstein, & Mosher, 1995), suggesting that perception of performance (peer-comparison and self-satisfaction) may require ego-involvement for the association with pathological self-reflection to occur. The FIQT may not incite strong ego-involvement, as it is framed as measuring visual perception (not academic skill, as previous tools have been) and was completed anonymously online. If so, the present experiment suggests that low ego-involved tasks may not have a strong relationship with MDD and GAD. The FIQT was largely unrelated to self-criticism, with the exception of the MDD group; the global negative self- and world- view typical of depression (Beck, 1967) may explain this. As such, the FIQT cannot currently be used as a proxy for existing self-criticism questionnaires as it may be measuring a form of negative self-reflection distinct from self-criticism; future work could consider comparison with a measure of perfectionism, as this behaviour is related to self-evaluation of performance (Stoeber, Hutchfield, & Wood, 2008).

6.5.1 Strengths, limitations & future directions

This sample was overall robustly powered, recruited from the general population and used well-validated measures of neuroticism and self-criticism. When divided by diagnosis the GAD group was small; though results were largely the same when a sensitivity analysis was conducted, the GAD group sample size was below that suggested in power calculations. Diagnosis was self-reported, without external confirmation or an analysis of severity. Though labelled as ‘dual’, no information about the timeline of diagnosis or recovery was given. Chronology of MDD and GAD onset may be important, as there is evidence to suggest preceding anxiety a strong predictor of later depression but less evidence

to support the reverse when additional predictors are considered (Mathew, Pettit, Lewinsohn, Seeley, & Roberts, 2011) . Use of a general population sample is advantageous in understanding variations outside of clinical settings, but the present findings require confirmation in groups with clear diagnostic categorisation. Future work would benefit from including current severity measures of disorders, to assess whether the observed relationships are affected by this factor.

Future work should explore the key contributions of neuroticism and self-criticism to pathology in a wider range of psychopathological conditions. For example, there is evidence that both these traits are raised in bipolar disorder, PTSD and borderline personality disorder (Kopala-Sibley et al., 2015). The latter may be of particular interest, as personality disordered individuals are often among the most complex to treat for additional axis 1 disorders (Pliner & Haddock, 1996). Indeed, self-reflection can be considered as a spectrum, with highly negative levels in disorders such as MDD, anxiety and eating disorders (Blatt, 2004; Dunkley & Grilo, 2007) through to diminished or pathological low levels in autism & schizophrenia (Philippi & Koenigs, 2014), with healthy populations somewhere in between (Bradley et al., 2016). Building on previous work (Bagby et al., 2008), these findings suggest the potential of neuroticism, pro-social traits and lower-order individual differences such as self-hatred in patient stratification for more tailored personalised interventions. The ability to easily and cheaply identify individuals more likely to respond to pharmacotherapeutic interventions or more likely to benefit from compassion-centred therapy early on in their treatment process would be both time and cost effective for clinical services.

6.6 Conclusion

This study highlights additional information available by looking beyond broad-domain characteristics in populations at risk of affective disorders. Neuroticism is a clear broad-domain risk factor for mood and anxiety disorders, whilst differences in self-critical attitude and pro-social traits show promise in both identification and treatment of MDD, GAD and those at risk of multiple diagnosis. Self-hatred appears specifically raised in individuals who have experienced multiple affective disorder diagnoses, which has relevance to the identification and treatment of particularly vulnerable groups. Further, the potential for patient stratification for provision of tailored personalised interventions using personality

traits is shown. Future work involving more specific diagnostic categories is required to support these findings. Piloting of the FIQT in a psychiatrically-relevant population suggests that the tool measures a form of negative self-reflection that is somewhat separate from self-criticism.

Chapter 7: Neuroticism in the vulnerable dark triad and individual differences in expression of emotional instability and interpersonal antagonism.

7.1 Chapter summary

The Vulnerable Dark Triad (VDT) is a set of commonly co-occurring personality constructs (Miller, Dir, et al., 2010; Paulhus & Williams, 2002). The VDT consists of vulnerable narcissism, secondary psychopathy and Borderline Personality Disorder (BPD) traits (Miller, Gentile, & Campbell, 2013). The triad constructs are conceptually united by characteristic emotional vulnerability, affective instability and interpersonal antagonism (Miller, Dir, et al., 2010). Closely linked to VDT characteristics such as emotional instability and affective distress (Lahey, 2009), neuroticism is a broad-domain personality trait proposed to form the ‘core’ of the VDT (Miller, Dir, et al., 2010). Self-esteem (Miller et al., 2013) and anxiety (Durand & Plata, 2017; Newman, MacCoon, Vaughn, & Sadeh, 2005) are key associates linked to the VDT, and are additionally connected to neuroticism (Clark et al., 1994) (Lahey, 2009). The majority of research to date has focused on the Dark Triad, with far less work exploring the mechanisms involved in the VDT. Indeed, aside from the original research by Miller et al (Miller, Dir, et al., 2010) much of the research exploring neuroticism as the ‘core’ of the VDT has only explore this trait in the context of a single construct (e.g. comparing vulnerable and grandiose narcissism, (Miller et al., 2017; Rogoza, Wyszynska, Maćkiewicz, & Ciecuch, 2016) or primary and secondary psychopathy (Douglas, Bore, & Munro, 2012). As such, there is a paucity of clear replication in this area, as well as an absence of consideration of interaction with lower order traits (such as self-criticism or self-esteem) in neuroticism and the VDT.

Following, this experiment investigated neuroticism as the ‘core’ of the VDT through exploration of the expression of VDT constructs and their interaction with self-perception and anxiety, when participants were grouped by high vs. low neuroticism scores. Further, the relationship between neuroticism and the characteristic traits of the VDT (emotional instability and interpersonal antagonism in particular) between constructs was explored. Building on chapter 6, this chapter also takes a multi-

level approach to understanding behaviour, exploring self-reflection as a lower-level facet. Participants scoring 1 standard deviation above or below average (as determined in chapter 3) on a measure of neuroticism were recruited. A total of 41 individuals completed self-report measures of the VDT and anxiety, with each participant's score on a measure of self-criticism, self-perception and the rest of the Big-5 personality traits (openness, conscientiousness, extraversion and agreeableness) made available from the experiment described in chapter 6, with their consent.

The results indicated greater numbers of individuals meeting the criteria for high levels of each VDT construct in high relative to low neuroticism. Additionally, findings suggest that neuroticism was distinctly associated with VDT characteristics in each of the constructs: neuroticism level was associated with significant differences in emotional instability-based questions in vulnerable narcissism, with interpersonal antagonism questions in secondary psychopathy, and with both emotional instability and interpersonal antagonism in BPD traits. The relationship between self-critical attitude and VDT construct scores was increased in those with high neuroticism. Self-hatred was consistently linked to the VDT, indicating the strong malignancy of the VDT. Further, as other self-critical and self-perception scores were not consistent across the VDT constructs, self-hatred may be a unifying attitude across the VDT. The results broadly support neuroticism as integral to the VDT (Miller, Dir, et al., 2010), and corroborate previous work suggesting neuroticism is a transdiagnostic factor in mental health pathology (e.g. Lahey, 2009). Post-hoc analysis hinted at a possible role of agreeableness in the VDT constructs, though further work is required given the discussed limitations of the present sample.

7.2 Introduction

The Vulnerable Dark Triad (VDT) consists of three commonly co-existing maladaptive personality constructs (Miller, Dir, et al., 2010) associated with psychological distress and both internalizing and externalizing disorders (Miller, Dir, et al., 2010; Pincus et al., 2009). The VDT consists of vulnerable narcissism, borderline personality disorder (BPD) traits and secondary psychopathy (Miller, Dir, et al., 2010). The vulnerable narcissism construct arises from a need for admiration and constant feedback as a method of maintaining poor self-worth and low self-esteem (Miller, Dir, et al., 2010; Pincus et al.,

2009), whereas secondary psychopathy is typified by impulsivity and emotional reactivity (Douglas et al., 2012; Newman et al., 2005). BPD traits centre on fear of abandonment and somewhat encompass characteristics of both of the other constructs through characteristic affective instability, emotional reactivity and impulsivity (Skodol et al., 2002; Wink, 1991). Emotional instability, affective volatility and interpersonal antagonism are key unifying characteristics of the VDT (Miller, Dir, et al., 2010). The VDT can be harmful, as indicated by increased risk of suicide and non-suicidal self-harm in those with high levels of the VDT constructs (Grigoras & Wille, 2017; Lieb, Zanarini, Schmahl, Linehan, & Bohus, 2004; Miller, Dir, et al., 2010).

The VDT was first developed in response to high heterogeneity in the Dark Triad (DT) constructs of grandiose narcissism, primary psychopathy and Machiavellianism (Miller, Dir, et al., 2010). Heterogeneity was so high in the DT that a two-factor approach to psychopathy has become commonly accepted (Newman et al., 2005), with evidence to support a two-factor approach to narcissism growing (Miller & Campbell, 2008). These two-factor approaches reflect a separation within psychopathy and narcissism in to the DT and VDT constructs, such that vulnerable narcissism and secondary psychopathy sit within the VDT, and grandiose narcissism and primary psychopathy within the DT (Miller, Dir, et al., 2010). A commonality in the two-factor models of both psychopathy and narcissism is a distinction between the antagonistic and dominant interpersonal styles typical of the DT constructs of primary psychopathy and grandiose narcissism (Watts, Waldman, Smith, Poore, & Lilienfeld, 2017) and the emotional instability typical of the VDT constructs of secondary psychopathy and vulnerable narcissism (Miller, Dir, et al., 2010). Following, there have been suggestions that the VDT and DT constructs are on a continuum (i.e. vulnerable narcissism – grandiose narcissism, secondary psychopathy – primary psychopathy, BPD - Machiavellianism) (Miller, Dir, et al., 2010) though this is not unanimously accepted (e.g. in Jonason, Li, & Buss, 2010).

Despite this split, there is some suggestion that VDT constructs remain heterogeneous in key characteristic expression (Kopala-Sibley, Zuroff, Russell, Moskowitz, & Paris, 2012). Variations in emotional security or interpersonal rejection have been shown in BPD (Bornstein, Becker-Matero, Winarick, & Reichman, 2010) and may dictate symptom expression (Gunderson, 2007). Disparity in

types of self-critical attitude are also noted in BPD (Kopala-Sibley et al., 2012), with heterogeneity also shown in harm avoidance and impulsivity in secondary psychopathy (Docherty et al., 2016; Yildirim & Derksen, 2015). It has been suggested that higher-order (i.e. overarching) personality structures may be key to understanding heterogeneity, as a result of vulnerability to specific external stressors (arising from personality structure) can lead to exacerbation of particular behavioural or cognitive factors that are symptomatic of the constructs (Gunderson, 2007). This aligns with evidence that higher-order personality factors moderate affective and individual reactivity (Kopala-Sibley et al., 2012), interpersonal stress (Gunthert, Cohen, & Armeli, 1999; Liu & Alloy, 2010) and symptom expression within a range of clinical diagnoses (Malouff et al., 2005).

As high-order personality traits are thought to have a biological basis (e.g. Eysenck, 2017) and emerge in childhood (Rothbart & Ahadi, 1994), they may be considered precursors to profiles such as the VDT. The personality trait of neuroticism is highly related to negative emotionality, worry, anxiety, sadness, self-consciousness and vulnerability (Costa & McCrae, 1992; Lahey, 2009) and has been posited as the ‘core’ of the VDT (Jones & Figueredo, 2013; Miller et al., 2010). High levels of neuroticism are linked to disproportionate emotional responses (Costa & McCrae, 1992), a clear parallel to the emotional instability characteristic of the VDT (Jakobwitz & Egan, 2006; Miller, Dir, et al., 2010; Wink, 1991). Neuroticism it is also frequently associated with mood and anxiety disorders (Muris, Roelofs, Rassin, Franken, & Mayer, 2005) which have considerable co-morbidity with constructs such as BPD (Lieb et al., 2004), tying neuroticism to the VDT characteristic of affective vulnerability. In contrast, agreeableness has been posited as central to the DT (Jakobwitz & Egan, 2006), reflective of the proposed heterogeneity between the triads. Though there is a reasonable body of work exploring the role of broad-domain personality constructs in the DT (e.g. Jakobwitz & Egan, 2006; O’Boyle, Forsyth, Banks, Story, & White, 2015; Paulhus & Williams, 2002) far less research has focused explicitly on the VDT. This is despite an association between presence of VDT characteristics and negative outcomes such as maladjustment (Lieb et al., 2004) and psychological distress (Miller & Campbell, 2008).

Research has suggested that personality characteristics and traits co-existing with neuroticism may contribute to specific symptom profiles (Kopala-Sibley et al., 2012). As discussed in previous chapters,

this may partially explain the lack of specificity of neuroticism as a transdiagnostic risk factor when considered in isolation (Lahey, 2009; Rodriguez-Seijas et al., 2015). High levels of neuroticism are linked to greater anxiety and increased self-criticism (Clark et al., 1994; Lahey, 2009). Anxiety is proposed to be central to the VDT, as it may differentiate between secondary psychopathy and the Dark Triad counterpart of primary psychopathy (Neria et al., 2016). Anxiety is also innate in BPD traits and vulnerable narcissism (Lieb et al., 2004; Miller et al., 2017). Self-criticism, other-orientated concerns and perfectionism are all associated with both vulnerable narcissism (Stoeber, Sherry, & Nealis, 2015) and BPD (American Psychiatric Association, 2013) and may have important relationships with the VDT. Given the strong links between neuroticism, anxiety and self-criticism and the presence of these traits in the VDT, understanding the relationship between neuroticism and co-existing traits in the VDT could explain additional risk. For example, BPD in particular is associated with suicide risk (Zanarini et al., 2003) and self-destructive behaviour (Bornstein et al., 2010). Evidence suggests that both neuroticism (Morey & Zanarini, 2000) and self-criticism (St. Germain & Hooley, 2012) increase risk of non-suicidal self-injury. Relationships like this may indicate that high neuroticism and high self-criticism are a particularly potent combination and may underlie constructs such as BPD. As such, a multi-level approach to understanding the VDT could be highly informative.

Some researchers approach the VDT as homogenous constructs, creating a composite VDT score (e.g. Jonason, Li, & Buss, 2010). However, composite scores may hide important relationships with external factors held by the constructs independently (Lilienfeld, Watts, Francis Smith, Berg, & Latzman, 2015; Watts et al., 2017), and though there may be a common core, differential relationships between dark personality constructs and other higher-order traits are present (Miller, Dir, et al., 2010; Watts et al., 2017). Further, VDT constructs are heterogenous not only in their relation to other traits and each other, but in their symptom expression and clinical associations (Docherty et al., 2016; Gunderson, 2007; Kopala-Sibley et al., 2012). Exploration not only of the role of neuroticism within each construct, but also how it relates to the key characteristics of the VDT (i.e. emotional instability and interpersonal antagonism) across questionnaire measures could provide insight in to the structure and role of this potentially overarching trait. It would be informative to understand whether neuroticism relates more

closely to the emotional instability rather than interpersonal antagonism characteristics of the VDT, as the role of this and other overarching traits may have been hidden by a construct-level approach. Interpersonal antagonism might be considered closely related to the high-order trait of agreeableness due to their polar opposition (McCrae & Costa, 1987); full analysis of the role of neuroticism in both characteristics is crucial before conclusions about the ‘core’ of the VDT can be drawn.

7.2.1 Aims & hypotheses

Due to suggestions that neuroticism is the ‘core’ of the VDT, vulnerable narcissism, secondary psychopathy and BPD traits were explored in individuals selected for high or low neuroticism scores. It is expected that individuals with higher neuroticism scores will show greater scores across the VDT. The role of neuroticism in the VDT at a characteristic (i.e. emotional/affective instability and interpersonal antagonism) level was also explored, by looking at the role of neuroticism within each questionnaire set. Neuroticism was predicted to relate highly to the emotional and affective instability characteristics of the VDT, but less strongly to questions tapping interpersonal antagonism. As outlined above, neuroticism is closely associated with both self-criticism and anxiety (Coyne & Whiffen, 1995; Lahey, 2009), which also have links to the VDT (Lieb et al., 2004; Miller, Dir, et al., 2010; Stoeber et al., 2015). As such, it was predicted that high levels of neuroticism should also indicate stronger associations between the VDT constructs and both anxiety and self-criticism.

7.3 Methods

7.3.1 Participants

Participants were recruited from a larger online experiment involving any adult (18-99 years of age) with internet access and fluent English ability (see chapter 6 for full details). Participants were selected from the online experiment completers based on neuroticism scores of 1 standard deviation above (female ≥ 65 , male ≥ 58) or below (female ≤ 32 , male ≤ 26) population average. Ethical approval was granted by King’s College London (RESCMR-16/17-4080) and all participants gave written informed consent.

7.3.2 *Materials*

7.3.2.1 Hypersensitive Narcissism Scale

The Hypersensitive Narcissism Scale (HSNS; Hendin & Cheek, 1997) is a ten item self-report measure of hypersensitive narcissism. Participants respond to questions about characteristics, feelings and behaviour with a Likert scale of 1-5 (very uncharacteristic- very characteristic).

7.3.2.2 Levenson Self-Report Psychopathy Scale

The Levenson Self-Report Psychopathy Scale (LSRP; Levenson, Kiehl, & Fitzpatrick, 1995) is a 26-item measure of primary and secondary psychopathy, consisting of statements participants respond to with a scale of 1-5 (strongly disagree- strongly agree).

7.3.2.3 MacLean Screening Instrument for Borderline Personality Disorder

The MacLean Screening Instrument for Borderline Personality Disorder (BPD; Zanarini et al., 2003) is a self-report questionnaire consisting of 10 items about personal history. Participants give yes or no responses.

7.3.2.4 Fear Survey Schedule

The Fear Survey Schedule (FSS; Wolpe & Lang, 1969) is a 108 self-report items regarding fear proneness, participants respond to a series of potentially fear-inducing things/experiences with how disturbing they find each item on a Likert scale of 0-4 (not at all – very much).

7.3.2.5 The Trait Self-Description Inventory

The Trait Self-Description Inventory (TSDI; Collis & Elshaw, 1998) is a 50-item self-report questionnaire measuring the Big-5 personality traits of openness (to experience), conscientiousness, extraversion, agreeableness and neuroticism. Participants completed this measure in a previous experiment (see chapter 6).

7.3.2.6 Forms of Self-Criticising/Attacking and Self-Reassuring Scale

The Forms of Self-Criticising/Attacking and Self-Reassuring Scale (FSCRS; Gilbert, Clarke, Hempel, Miles, & Irons, 2004) consists of a 22-item scale, exploring tendency to be self-critical or self-reassuring in personal setbacks and failures. The inadequate-self and hated-self subscales are totalled to give an overall self-criticism score (Baião et al., 2015). FSCRS data was collected from the participants in a previous experiment (see chapter 6).

7.3.2.7 The Fake IQ Test

The Fake IQ Test (FIQT) is measure of self-perception adapted from an original tool designed by Nuttin & Greenwald (1968), as outlined in chapter 6. The FIQT is presented to participants as a measure of visual perception requiring comparative judgements about visual stimuli (i.e. which shape is larger, or which line is longer) displayed side-by-side on screen (see chapter 6 materials section for examples). Though designed to plausibly have measurable differences, the items are identical and thus there is no correct answer. Participants are not given any feedback on their performance. Participants rate their satisfaction with their performance (self-satisfaction) and how well they believe they have performed relative to peers (peer-comparison) on a 4-point Likert scale after every block of 5 image pairings, completing 9 blocks in total (45 image pairings). See Figure 14 in the previous chapter for stimuli examples. The FIQT data was collected in a previous experiment (see chapter 6).

7.3.3 *Design*

Participants attended a one-hour session on site at the Institute of Psychiatry, Psychology & Neuroscience in South London, where they completed the HSNS, BPD, LSRP and FSS questionnaires (the FSCRS, FIQT and TSDI measures were completed by participants in a previous online experiment, as detailed in chapter 6). They were paid for their time in line with King's College London procedures.

7.3.4 Statistical analysis

SPSS (IBM; Chicago, US) was used for all analysis. Between group (high vs. low neuroticism scorers) differences were explored with one-way ANOVA except for comparison of individual question scores in the MacLean BPD measure which required a X^2 analysis due to yes/no responding.

7.3.4.1 Power calculations

Power calculations using G*Power suggest a minimum sample size of 24 for identification of large effect sizes in one-way ANOVA ($1-\beta = .95$, $\alpha = .05$, $d = .80$) and 31 for X^2 analysis ($1-\beta = .95$, $\alpha = .05$, $d = .80$). Suggested sample sizes for moderate effect size were higher at 88 individuals per group for a one-way ANOVA ($1-\beta = .95$, $\alpha = .05$, $d = .50$) and 220 per group for X^2 analysis ($1-\beta = .95$, $\alpha = .05$, $d = .30$). Bivariate correlations were conducted on each group separately (requiring a sample size of 115; $1-\beta = .95$, $\alpha = .05$, correlation of 0.3) (Faul et al., 2009, 2007). These calculations reflect the planned comparisons outlined in section 7.2.1.

7.4 Results

Forty-one individuals (29 female) aged 18-43 ($M = 24.61$, $SD = 5.75$) completed the present experiment. The sample consisted of a roughly even split of high ($n = 19$) and low ($n = 22$) trait neuroticism scorers. Table 19 shows the average scores for each group (high vs. low neuroticism) across the main variables of interest (FIQT-satisfied, FIQT-peer, FSCSRS self-hatred, self-inadequacy and self-reassurance, anxiety, vulnerable narcissism, BPD traits and primary and secondary psychopathy; average scores for the rest of the Big-5 (i.e. openness, conscientiousness, extraversion and agreeableness) are also shown. Data was tested for normality in each group (high neuroticism, low neuroticism), producing acceptable levels of skew and kurtosis (Field, 2013). A one-way ANOVA was also conducted, indicating significant differences between groups on all measures except for the FIQT scales and primary psychopathy.

Table 19

ANOVA comparison of perception of performance, self-criticism and anxiety in those with high vs. low neuroticism scores

	<i>f</i>	<i>p</i>	Low Neuroticism M (SD)	High Neuroticism M (SD)
FIQT-Satisfied	.324	.573	24.8 (5.6)	23.7 (6.1)
FIQT-Peer	3.30	.077	25.0 (5.0)	22.4 (4.0)
FSCSRS Hatred-self	31.99	<.001**	1.0 (1.4)	9.0 (6.4)
FSCSRS Inadequate-self	81.86	<.001**	12.36 (5.3)	28.6 (6.2)
FSCSRS Reassure-self	60.82	<.001**	24.8 (2.7)	12.2 (7.0)
Vulnerable Narcissism (HSNS)	18.64	<.001**	24.9 (6.5)	32.5 (4.2)
Borderline Personality traits (MS)	41.04	<.001**	1.2 (2.0)	5.3 (2.0)
Primary Psychopathy (LSRP)	.415	.523	28.1 (7.7)	26.7 (5.5)
Secondary Psychopathy (LSRP)	7.20	.011*	18.2 (3.5)	21.7 (4.8)
Anxiety (FSS)	5.85	.020*	56.1 (52.7)	121.1 (37.2)
Openness	2.26	.141	43.7 (11.4)	48.6 (9.2)
Conscientiousness	1.34	.253	57.0 (11.6)	52.6 (12.5)
Extraversion	7.81	.008*	4.1 (11.7)	-5.2 (9.1)
Agreeableness	.126	.725	46.2 (11.9)	47.5 (10.3)

* Significant at .05

** Significant at .001

ANOVA, analysis of variance; FIQT, Fake IQ Test; FSCSRS, Forms of Self-Criticising Self-Reassuring Scale; HSNS, Hypersensitive Narcissism Scale; MS, MacLean Scale; LSRP, Levenson Self-Report Psychopathy scale; FSS, Fear Survey Schedule

As several the behavioural facets being explored are linked to gender (e.g. higher neuroticism scores in females; Lahey, 2009) a further ANOVA was conducted when controlling for gender. No significant differences were observed between male and female groups on any measure in the low or high neuroticism groupings (all $p > .05$).

Cut-off values for above average vulnerable narcissism (mean populations scores; Hendin & Cheek, 1997), BPD traits (Zanarini et al., 2003) and primary and secondary psychopathy (mean population

scores; Levenson et al., 1995) were applied to the data to investigate differences in self-criticism and performance perception dependent on presence of VDT traits. Significant differences in self-critical attitude were shown in BPD and vulnerable narcissism but differences were less consistent in primary and secondary psychopathy. No significant difference in anxiety scores were present in any of the VDT traits or primary psychopathy. See Table 20 for full details.

Table 20

ANOVA comparison of perception of performance, self-criticism and anxiety in those with high vs. low VDT scores

	Vulnerable narcissism		BPD		Primary psychopathy		Secondary psychopathy	
	f	p	f	p	f	p	f	p
FIQT-Self	2.14	.151	.393	.534	1.42	.241	.861	.359
FIQT-Peer	.000	.985	3.77	.059	1.08	.305	.037	.849
FSCSRS-Hatred	7.68	.008*	17.81	.000**	5.37	.026*	3.87	.056
FSCSRS-Inadequate	11.19	.002**	8.55	.006*	2.75	.106	4.50	.040*
FSCSRS-Reassure	10.33	.003**	6.65	.014*	1.20	.280	3.86	.057
FSCSRS-Total	11.55	.002**	13.54	.001**	4.17	.048*	4.93	.032
Anxiety (FSS)	3.48	.070	3.47	.070	.919	.344	3.193	0.82

* Significant at .05

** Significant at .005

BPD; borderline personality disorder (traits); FIQT, Fake IQ Test; FSCSRS, Forms of Self-Criticising and Self-Reassuring Scale; FSS, Fear Survey Schedule.

The number of individuals in each group (high vs. low neuroticism) meeting the criteria for above average levels of VDT traits was explored. An ANOVA was used to assess whether the number of individuals with raised scores was significantly different between the groupings. Results are shown in Figure 15, with a significant difference in number of above average scorers between groups shown in vulnerable narcissism and secondary psychopathy. Though the difference in the number of individuals scoring above average on the BPD measure was not significant, it was very close ($p = .051$).

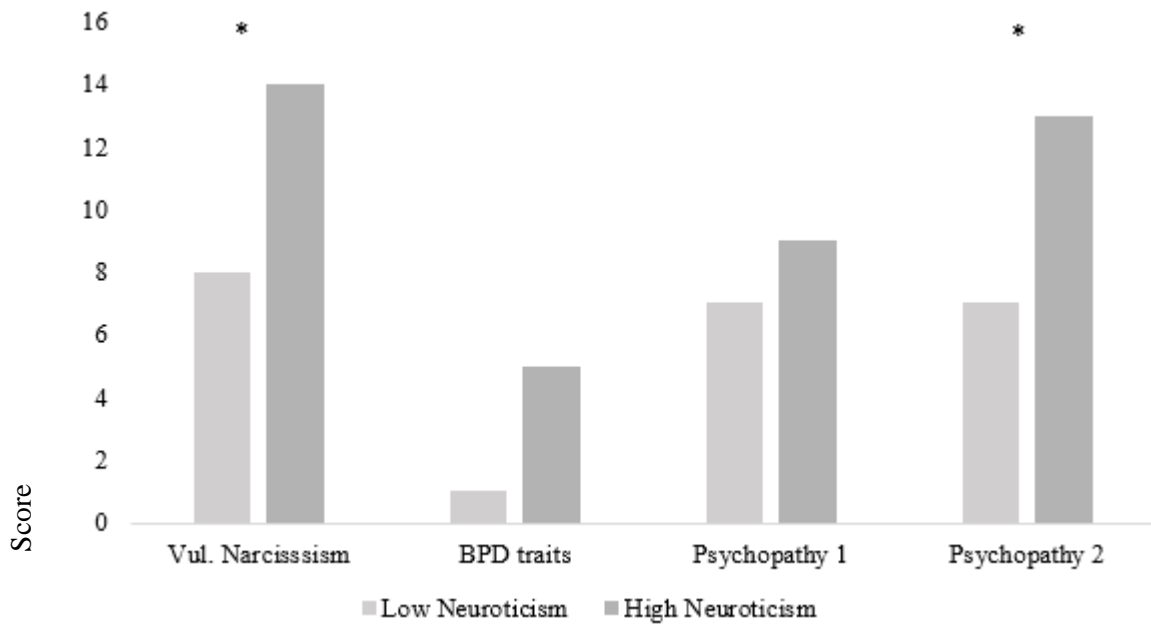


Figure 15 Number of individuals with above average scores in vulnerable narcissism, BPD and primary and secondary psychopathy in high vs. low neuroticism groupings

Correlations between variables in high vs. low neuroticism were explored as shown in Table 21, below. Results suggest a significant positive relationship between primary psychopathy and ratings of self-satisfaction and peer-comparison in the low neuroticism group, such that higher primary psychopathy ratings are associated with higher feelings of satisfaction and higher valuing of self over peers. There was additionally a relationship between secondary psychopathy and self-satisfaction. Differentiations between neuroticism groups were also present between feelings of inadequacy and self-hatred and vulnerable narcissism and secondary psychopathy. As shown in Figure 16 below Table 21, vulnerable narcissism showed stronger self-reassurance and lower feelings of inadequacy in the low neuroticism group. Anxiety (fear-proneness) only correlated with BPD traits and vulnerable narcissism in the low and high neuroticism groups respectively. The VDT constructs had moderate-to-strong correlations with each other, regardless of neuroticism level.

Table 21

Correlations between variables in individuals with low (top row within cell) vs high (bottom row within cell) neuroticism groupings

	FIQT-Satisfied	FIQT-Peer	Hatred-Self	Inadequate-Self	Reassure-Self	Vul. Narcissism	BPD traits	Primary psychopathy	Secondary psychopathy
FIQT-Peer	.667*	-	-	-	-	-	-	-	-
	.711**	-	-	-	-	-	-	-	-
FSCSRS Hatred-Self	-.302	-.122	-	-	-	-	-	-	-
	.188	-.187	-	-	-	-	-	-	-
FSCSRS Inadequate-Self	-.194	-.303	.185	-	-	-	-	-	-
	.000	-.189	.562**	-	-	-	-	-	-
FSCSRS Reassure-Self	.153	-.047	-.340	-.129	-	-	-	-	-
	-.351	.243	-.597**	-.380	-	-	-	-	-
V. Narcissism	.290	.247	.139	.311	-.391	-	-	-	-
	.387	.017	.525*	.558*	-.573*	-	-	-	-
BPD traits	.265	.062	.522*	.163	-.311	.602**	-	-	-
	.314	-.030	.591**	.458*	-.451	.664**	-	-	-
Primary psychopathy	.547**	.552**	.053	-.046	.056	.561**	.373	-	-
	.070	.166	.039	-.049	.262	.322	.106	-	-
Secondary psychopathy	.497*	.349	.251	.056	-.220	.767**	.664**	.791*	-
	.065	-.256	.482*	.388	-.441	.625**	.633**	.483*	-
Anxiety (FSS)	-.054	.069	.202	.072	-.410	.350	.445*	.067	.293
	.256	.366	.242	.203	-.013	.488*	.262	.352	.272

* Significant at .05 level

** Significant at .001 level

FIQT-S, Fake IQ Test-Satisfied; FIQT-P, Fake IQ Test-Peer comparison; FSCSRS, Forms of Self-Criticising and Self-Reassuring Scale; V. Narcissism, vulnerable narcissism; BPD, borderline personality disorder; FSS, Fear Survey Schedule.

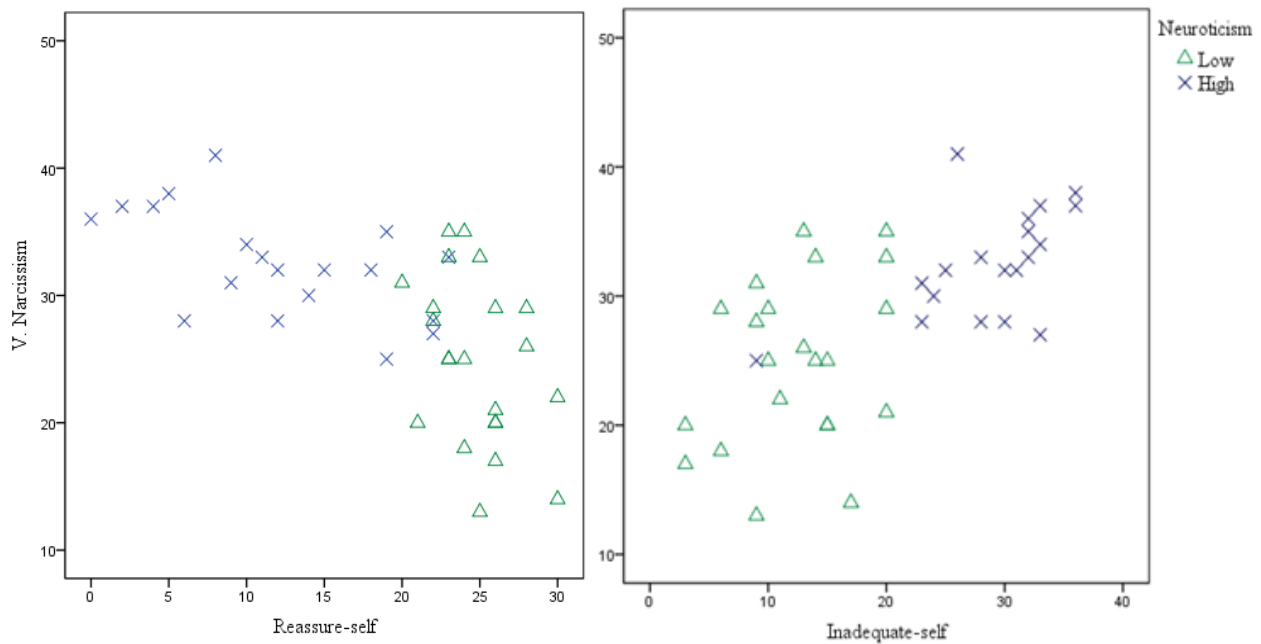


Figure 16 Self-reassurance and self-inadequacy associations with vulnerable narcissism score, dependent on neuroticism grouping (high vs. low scorers)

As differences in total scores for vulnerable narcissism, BPD and secondary psychopathy were observed between high and low neuroticism scorers, the role of neuroticism at the question level was explored within these measures to assess whether neuroticism is related to the characteristics of the VDT (i.e. emotional/affective instability and interpersonal antagonism) within each construct (i.e. vulnerable narcissism, BPD traits and secondary psychopathy). Significant differences in scores were shown for most of questions on the HSNS (vulnerable narcissism) and MacLean (BPD traits) questionnaires dependent on neuroticism level, as shown in Figure 17, below. Given the response structure of the MacLean (borderline personality traits) questionnaire (participants answered with yes/no responses), a chi-square test of significance was applied to this data. 90% of the MacLean (BPD) questions differed significantly between neuroticism groups, compared to 60% of the HSNS (vulnerable narcissism) and 36% of the LRSP (secondary psychopathy) questions. Secondary psychopathy was far more split, with fewer than half of the questions showing significant differences in high vs. low neuroticism scorers; see Table 22 for more information and the details of individual questions. Overall, differences in neuroticism appeared to have the largest reflection in BPD, with significant differences between the groups in all but one question.

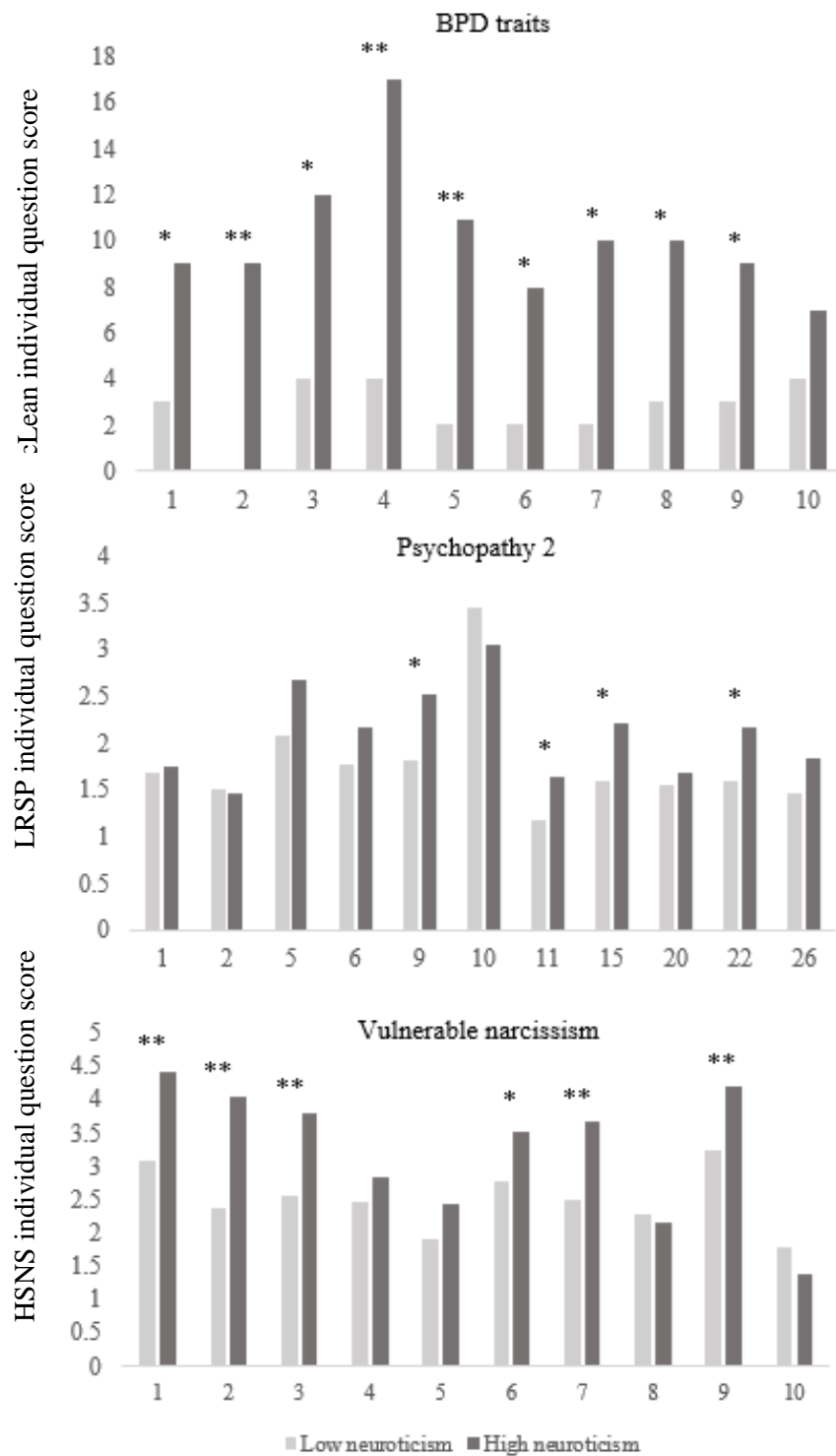


Figure 17 Question-level analysis of difference in score depending on neuroticism grouping (high vs. low scorers), for Borderline Personality Disorder (BPD), secondary psychopathy and vulnerable narcissism

Table 22

Average scores and ANOVA/Chi-squared tests of difference between high vs low neuroticism scorers on each question of scales measuring VDT constructs

	Low N		High N		f	p
Vulnerable narcissism (HSNS)	M	SD	M	SD		
1. I can become entirely absorbed in thinking about my personal affairs, my health, my cares or my relation to others	3.09	1.07	4.42	.838	19.30	<.001**
2. My feelings are easily hurt by ridicule or the slighting remarks of others	2.36	1.18	4.05	.621	31.474	<.001**
3. When I enter a room I often become self-conscious and feel that the eyes of others are on me	2.55	.739	3.79	.918	23.122	<.001**
4. I dislike sharing the credit of achievement with others	2.45	1.18	2.84	1.21	1.067	.308
5. I feel that I have enough on my hands without worrying about other people's troubles	1.91	.750	2.42	1.17	2.859	.099
6. I feel that I am temperamentally different from most people	2.77	1.11	3.53	1.07	4.845	.034*
7. I often interpret the remarks of others in a personal way	2.50	.964	3.68	1.11	13.402	.001**
8. I easily become wrapped up in my own interests and forget the existence of others	2.27	1.28	2.16	1.21	.086	.771

Vulnerable narcissism (HSNS)	Low N		High N		f	p
	M	SD	M	SD		
9. I dislike being with a group unless I know that I am appreciated by at least one of those present	3.23	1.31	4.21	.855	7.842	.008*
10. I am secretly “put out” or annoyed when other people come to me with their troubles, asking my for my time and sympathy	1.77	1.02	1.37	.597	2.298	.138
Secondary psychopathy (LRSP)						
1. Before I do anything, I carefully consider the possible consequences	1.68	.568	1.74	.872	.059	.810
2. Cheating is not justified because it is unfair to others	1.50	.598	1.47	.612	.019	.890
5. I am often bored	2.09	.971	2.68	1.0	3.691	.062
6. I don’t plan anything very far in advance	1.77	.973	2.16	1.26	1.219	.276
9. I find myself in the same kinds of trouble, time after time	1.82	.958	2.53	1.02	5.246	.027*
10. I find that I am able to pursue one goal for a long time	3.45	.912	3.05	1.02	1.764	.192
11. I have been in a lot of shouting matches with other people	1.18	.395	1.63	1.03	5.125	.029*
15. I quickly lose interest in tasks I start	1.59	.666	2.21	.831	5.765	.021*
20. Love is overrated	1.55	.739	1.68	.976	.278	.601

Secondary psychopathy (LSRP)	Low N		High N			
	M	SD	M	SD	f	p
22. Most of my problems are due to the fact that other people just don't understand me	1.59	.854	2.16	.898	4.283	.045*
26. When I get frustrated, I often "let off steam" by blowing my top	1.45	.596	1.84	.834	2.989	.092
BPD (MacLean)	No (N)	Yes (N)	No (N)	Yes (N)	X ²	p
1. Have any of your closest relationships been troubled by a lot of arguments or repeated breakups?	19	3	10	9	5.604	.021*
2. Have you deliberately hurt yourself?	22	0	10	9	13.352	<.001**
3. Have you had at least two other problems with impulsivity (e.g. eating binges and spending spree...)?	18	4	7	12	8.667	.004**
4. Have you been extremely moody?	18	4	2	17	20.739	<.001**
5. Have you felt angry a lot of the time?	20	2	8	11	11.214	.001**
6. Have you often been distrustful of other people?	20	2	11	8	6.026	.017*
7. Have you frequently felt unreal or as if things around you were unreal?	20	2	10	9	7.609	.007*
8. Have you chronically felt empty?	19	3	9	10	7.159	.009*

BPD (MacLean)	Low N		High N		X ²	p
	No (N)	Yes (N)	No (N)	Yes (N)		
9. Have you often felt you have no idea of who you are or that you have no identity?	19	3	10	9	5.604	.021*
10. Have you made desperate efforts to avoid feeling abandoned or being abandoned (e.g. repeatedly calling someone...)	18	4	12	7	1.808	.161
N, neuroticism; HSNS, Hypersensitive Narcissism Scale; BPD, borderline personality disorder						
* Significant at .05						
** Significant at .005						

7.4.1 Post-hoc analysis

A small post-hoc additional to the analysis was made. Correlational relationships between the remaining big-5 traits (openness, conscientiousness, extraversion & agreeableness) and the VDT constructs was conducted, as previous work has suggested other overarching personality traits may play a role in in dark personality constructs (Jakobwitz & Egan, 2006; Miller, Dir, et al., 2010). This analysis was conducted as an indicator of potential relationships; as the sample were selected for the associated trait of neuroticism, further interpretation is not possible. The results of these correlations are shown in Table 23. Results indicate a negative relationship between conscientiousness and vulnerable narcissism and secondary psychopathy, a positive relationship between extraversion and primary psychopathy and a negative relationship between agreeableness and both forms of psychopathy.

Table 23

Correlations between big-5 traits (aside from neuroticism) and VDT constructs, across the whole sample (n = 41)

	Vul. Narcissism	BPD traits	Primary psychopathy	Secondary psychopathy
Openness	.126	.148	.038	-.029
Conscientiousness	-.372*	-.215	-.166	-.492**
Extraversion	-.289	-.283	.363*	-.151
Agreeableness	-.312	-.078	-.530**	-.458**
* Significant at .05				
** Significant at .001				

Of the remaining big-5 traits, agreeableness in particular is posited as potentially being involved in VDT construct expression (Jensen-Campbell & Graziano, 2001). Following, the sample were divided in to two groups: high vs. low agreeableness, split by sample average score (mean = 46.8, SD = 11.1).

Analysis of difference in individual question scores dependent on agreeableness group membership (high vs. low) was conducted, to assess whether agreeableness might relate to those questions not significantly related to neuroticism score in Figure 17, above. Analysis indicated that differing levels of agreeableness related to significant differences in a few of the questions that were shown not to differ in average scored dependent on neuroticism level. Specifically, those with high levels of agreeableness had significantly lower scores on questions 5 ($f(1, 39) = 10.082, p = .003$) and 10 ($f(1, 39) = 6.713, p = .002$) of the HSNS measure of vulnerable narcissism; additionally, higher agreeableness was associated with significantly lower scores on questions 20 ($f(1, 39) = 10.634, p = .002$), 22 ($f(1, 39) = 6.423, p = .015$) and 26 ($f(1, 39) = 5.740, p = .021$) of the LRSP measure of secondary psychopathy. No significant difference in individual questions scores on the MacLean measure of BPD were observed between high and low agreeableness scorers when a chi-squared analysis was conducted. Details of the questions are shown in Table 22. With the exception of LRSP question 22, these differences were not shown when dividing the group by neuroticism (see Figure 17).

As the sample were originally selected for high and low levels of neuroticism, correlations between full-scale agreeableness and each question of the VDT measures were checked for agreement with the above analysis. The results partially replicated those of the ANOVA tests above, indicating significant negative correlations between agreeableness and questions 5 ($r = -.599, p < .001$) and 10 ($r = -.665, p < .001$) of the HSNS measure of vulnerable narcissism, and between agreeableness and questions 20 ($r = -.409, p = .008$) and 26 ($r = -.399, p = .010$) of the LRSP measure of secondary psychopathy. As in the ANOVA analysis, no relationship between agreeableness and the MacLean measure of BPD traits was shown. In addition to these supportive findings, an additional small negative correlation between agreeableness and question 4 ($r = -.330, p = .035$) of the HSNS scale shown. Moreover, the correlation between question 22 of the LRSP and agreeableness did not quite reach significance ($r = -.305, p = .053$). These findings indicate caution should be applied when considering the role of agreeableness in the presented analysis.

Finally, correlations between agreeableness and scores on the primary psychopathy sub-scale of the LRSP were conducted in line with suggestions that (dis)agreeableness is a central feature of the DT.

The results of this analysis are shown in the table below (Table 24); no other DT measures were conducted in this experiment, so it was not possible to assess the role of agreeableness beyond primary psychopathy.

Table 24

Correlations between agreeableness and primary psychopathy subscale questions of the LRSP

LRSP question	R
3. Even if I were trying very hard to sell something, I wouldn't lie about it	.033
4. For me, what's right is whatever I can get away with	-.262
7. I enjoy manipulating other people's feelings	-.395*
8. I feel bad if my words or actions cause someone else to feel emotional pain	-.486**
12. My main concern is the bottom line	-.082
13. I make a point of trying not to hurt others in pursuit of my goals	-.328*
14. I often admire a really clever scam	-.330*
16. I tell other people what they want to hear, so they will do what I want	-.164
17. I would be upset if my success came at someone else's expense	-.201
18. In today's world, I feel justified doing anything I can get away with to succeed	-.402**
19. Looking out for myself is my top priority	-.521**
21. Making a lot of money is my most important goal	-.134
23. My main purpose in life is getting as many goodies as I can	-.187
24. People who are stupid enough to get ripped off usually deserve it	-.243
25. Success is based on survival of the fittest; I am not concerned about the losers.	-.567**
* Significant at .05	
** Significant at .001	

7.5 Discussion

Results indicate that though neuroticism does have an important relationship with the VDT, it is not equal across the three constructs that make up the triad. Significant differences in vulnerable narcissism, BPD traits and secondary psychopathy total scores were observed between high and low neuroticism scorers. Further, significantly greater numbers of individuals had above average vulnerable narcissism and secondary psychopathy scores in the high neuroticism group, though the BPD traits construct did not quite reach significance. In depth analysis revealed varied role for neuroticism in individual questions within each construct questionnaire. Though all three constructs had some relation to neuroticism, the MacLean (BPD traits) questionnaire had by far the strongest relationship with 9 out of 10 question scores significantly affected by neuroticism score. Neuroticism was also key in the HSNS (vulnerable narcissism) measure, affecting just over half of the questions. Conversely, the LRSP (secondary psychopathy) showed a smaller relationship with neuroticism at the individual question level, with only 4 of the 11 questions affected by neuroticism score.

Though secondary psychopathy total score significantly differed between the high and low neuroticism groups, few items on the secondary psychopathy scale were significantly related to neuroticism score. These items largely focus on interpersonal antagonism, for example: “I have been in lots of shouting matches with other people”, “Most of my problems are due to the fact that other people don’t understand me” and “I find myself in the same kinds of trouble, time after time” (Levenson et al., 1995), which is an integral aspect of secondary psychopathy. A larger number of items on the vulnerable narcissism scale were associated with neuroticism, but these were mostly associated with emotional instability and self-concern (e.g. “I often interpret the remarks of others in a personal way” and “My feelings are easily hurt by ridicule or the slighting remarks of others”; Hendin & Cheek, 1997), which are key features of this construct (Miller, Dir, et al., 2010). The HSNS individual questions that did not differ depending on neuroticism score were mostly related to interpersonal antagonism; for example: “I dislike sharing the credit of achievement with others”, “I feel that I have enough on my hands without worrying about other people’s troubles”, “...I forget the existence of others” and “...I am annoyed when others come to me with their troubles...” (Hendin & Cheek, 1997) (full examples of all questions are shown in Table

22). Both interpersonal antagonism and emotional instability are core characteristics of the VDT (Miller, Dir, et al., 2010; Wink, 1991); these findings indicate neuroticism has a different relationship with core characteristic expressions in these two related constructs.

High neuroticism in vulnerable narcissism may be more associated with self-concern and emotional instability, whereas in secondary psychopathy it has a stronger link to interpersonal issues. These observed attributes related to neuroticism are typical of each construct: (vulnerable) narcissism is typified by self-interest and emotional instability (American Psychiatric Association, 2013c; Annen et al., 2017) and secondary psychopathy is characterised in part by abnormal social and interpersonal behaviours (Miller, Dir, et al., 2010). Neuroticism could be enhancing negative co-existing features and temperamental characteristics of the individual resulting in symptom presentation, as has been suggested in the context of psychopathology more broadly (Claridge & Davis, 2001). This fits with the concept of neuroticism as a candidate trans-diagnostic risk factor (Lahey, 2009) and with diathesis-based theories proposing that personality structures interact especially with congruent stressors, leading to symptom profiles (Gunderson, 2007). Though Gunderson's (2007) work focused on BPD, the present study suggests relevance of this model in vulnerable narcissism and secondary psychopathy also.

Though the MacLean (BPD traits) questionnaire features many interpersonal questions that do link to neuroticism, the only question without a relationship has an interpersonal focus ("Have you made desperate attempts to avoid feeling abandoned or being abandoned"; Levenson et al., 1995). High scores on the MacLean emotional instability-based questions (e.g. "Have you been extremely moody?"; Levenson et al., 1995) all associated with high neuroticism. The HSNS (vulnerable narcissism) indicates an expression of neuroticism in individual concerns, the LRSP (secondary psychopathy) highlights neuroticism in interpersonal antagonism and the MacLean (BPD traits) has a strong interaction with neuroticism across both features. These features (interpersonal antagonism and emotional instability) may both be integral to symptom expression in BPD, unlike the degree of specificity shown in secondary psychopathy and vulnerable narcissism. Perhaps BPD traits is the most malignant arm of the VDT; analysis of the relative burden of each trait would be required to confirm this, though it is pertinent that of the triad BPD is the only construct to feature in the DSM (American Psychiatric Association,

2013c) (though narcissism is included as a personality disorder, the profile is more typical of grandiose narcissism than vulnerable and thus is linked to the DT rather than the VDT).

Though the present work explores only neuroticism, another factor may be responsible for expression of interpersonal antagonism in vulnerable narcissism, or emotional instability in secondary psychopathy. Exploratory post-hoc analysis tentatively examined this possibility, building on suggestions that low agreeableness is linked to the VDT characteristic of interpersonal antagonism in the literature (Jensen-Campbell & Graziano, 2001), suggesting that this might explain VDT characteristics not captured by neuroticism. Indeed, the results indicated that low agreeableness scores did have a relationship with aspects of secondary psychopathy and vulnerable narcissism that were not covered by neuroticism. Specifically, though interpersonal antagonism was related to neuroticism in secondary psychopathy, it was not in vulnerable narcissism. Perhaps neuroticism forms the core of key construct characteristic expression (e.g. interpersonal antagonism in secondary psychopathy) whilst alternative traits could explain less prominent characteristics (e.g. emotional instability in secondary psychopathy). Further, previous work has hinted that low agreeableness is integral to the DT (Jensen-Campbell & Graziano, 2001); exploratory analysis in this chapter indicated an inconsistent relationship between agreeableness and the primary psychopathy subscale of the LRSP questionnaire, only partially supporting this hypothesis. However, importantly participants were selected for inclusion in this chapter on the basis of neuroticism scores of one standard deviation above or below average. As such, the representativeness of this sample and their agreeableness scores is uncertain. Additionally, of the DT only primary psychopathy was possible to discuss in this analysis, and only as measured by the LRSP. Further work with a broader spectrum of individuals and DT constructs is required before more certain conclusions can be drawn. Additionally, the VDT was not examined at a dimensional level in the present analysis. This design was chosen as there is some evidence in the literature the important aspects of traits can be hidden by use of composite dimensional scores (Jonason & Jackson, 2016; Lilienfeld et al., 2015) resulting in underestimation of the relationship of trait to external factors (Miller & Campbell, 2008). However, an interesting progression of this research might be to contiguously include a dimensional approach.

At a broader level, post-hoc analysis was conducted to partially address comments that other overarching personality traits may be integral to the VDT. Results indicated that lower agreeableness was associated with higher scores on the measure of primary and secondary psychopathy but had no association with vulnerable narcissism or BPD when considered as whole constructs. As such, this only partially supports previous work that has suggested agreeableness as an integral shared trait in the VDT (Miller, Dir, et al., 2010). The remaining big-5 traits of conscientiousness, extraversion and openness were also explored in relation to the VDT constructs. Conscientiousness had a relationship with both secondary psychopathy and vulnerable narcissism suggesting this trait is an additional link across the VDT. However, as discussed above this is caveated by the selection of this sample for extremely high or low neuroticism, which limits ability to discuss other big-5 traits as representative and normative. As such, additional work involving general populations not selected based on personality trait scores is required.

These findings support neuroticism as a transdiagnostic core of the VDT, exaggerating the maladaptive traits associated with the specific characteristics of each construct. Further, splitting the sample by neuroticism level indicated significantly more individuals meeting the cut-off score for high levels of vulnerable narcissism and secondary psychopathy. Differences were not evidence in primary psychopathy, supporting this idea as it is not part of the VDT (Miller, Dir, et al., 2010). Though BPD traits did not meet significance this was by a very small margin and may be due in part to sample size as recruitment did not attain the planned sample sizes (see statistical analysis section of this chapter for more details). These findings reiterate the potential malevolence of neuroticism in personality as well as in clinical constructs as demonstrated elsewhere (see chapters 3 and 6). Previous work has suggested anxiety can discriminate between primary and secondary psychopathy (Neria et al., 2016; Newman et al., 2005), though unexpectedly anxiety (fear-proneness) was not shown to have a relationship with either factor in this experiment. Conversely, high neuroticism was shown to relate to greater numbers of individuals with high levels of secondary psychopathy than low neuroticism, which was not replicated in primary psychopathy. Perhaps neuroticism is a more accurate differentiator of psychopathy than anxiety, again supporting the concept of neuroticism as the core of the VDT. However, the present

experiment only focused on three VDT measures; before firm conclusions can be drawn repetition with a range of questionnaires is crucial. It would also be of interest to repeatedly administer the questionnaires within participants over a more longitudinal time-line, to determine the stability and robustness of these measures.

High neuroticism is also related to other negative outcomes. Positive correlations between self-hatred and both high self-inadequacy and poor self-reassurance were present in the high but not low neuroticism group, suggesting a particularly maladaptive profile. Further, self-hatred correlated with vulnerable narcissism and secondary psychopathy scores in the high neuroticism group only. Vulnerable narcissism (in highly neurotic individuals) has a particularly broad relationship with maladaptive self-critical attitude; this is unsurprising, given the characteristic fragile ego and dependency on external praise associated with vulnerable narcissism (Miller, Dir, et al., 2010), and the link between high neuroticism and poor self-reassurance (Neff et al., 2007). This latter point may have relevance to the need for external praise in vulnerable narcissism, arising for the low ability to self-reassure especially in those who also have high neuroticism. Self-criticism and neuroticism are widely associated with mental health pathology (Clara et al., 2003; Hermanto et al., 2016; Lahey, 2009). Aspects of the VDT also have high co-morbidity with other psychiatric disorders including major depression, anxiety disorders and eating disorders (Lieb et al., 2004) which may be compounded by neuroticism contributing to self-critical attitude. This adds support for neuroticism as part of a transdiagnostic risk-factor with disorder-specific characteristics arising due to co-existing traits (Robbins, Oliver, & Caspi, 1998; Rodriguez-Seijas et al., 2015), with links to co-morbidity (Lahey, 2009).

Contrary to predictions, perceptions of performance (FIQT) did not differ dependent on neuroticism score, nor did it correlate with vulnerable narcissism and BPD scores. Higher primary psychopathy scores were associated with higher self-satisfaction and higher valuing of self- relative to others in low neuroticism; secondary psychopathy also showed a positive association with self-satisfaction in the low neuroticism group, such that higher psychopathy scores were associated with higher self-satisfaction. This somewhat highlights the similarity between these constructs, supporting the idea of psychopathy

continuum (Miller, Dir, et al., 2010). Supportive of this, primary and secondary psychopathy had significant correlations with each other. Interestingly, this relationship was higher in the low neuroticism group. This might be explained by the low level of neuroticism involvement in primary psychopathy (Jakobwitz & Egan, 2006), meaning these scores have more in common with secondary psychopathy scores in lower neuroticism and supporting the idea of neuroticism as integral in the VDT. Of note, neither psychopathy form had much of a relationship with self-criticism other than a moderate correlation between secondary psychopathy and self-hatred in high neuroticism, and they were the only constructs to have a relationship with the FIQT.

FIQT scores were shown to increase with higher levels of psychopathy of either type, according to correlational analysis. Individuals with high levels of psychopathy have been shown to rank themselves more highly than others (Del Gaizo & Falkenbach, 2008), supporting the validity of the FIQT as a measure of performance perception. It might be expected that vulnerable narcissism would also be associated with higher FIQT scores due to the egocentricity associated with this construct (Miller, Dir, et al., 2010; Miller et al., 2017). This was not identified in the present experiment, though as discussed in chapter 6 the FIQT has little potential for ego-involvement, which might explain the absence of this relationship. Possibly grandiosity in primary and secondary psychopathy relies less on egoism, whereas vulnerable narcissism has a fragile ego at the centre and a greater focus on the self. Though not directly exploring egoism, narcissism and psychopathy have indeed been shown to differ in relation to self-esteem (Falkenbach, Howe, & Falki, 2013). Further research exploring ego-involvement in DT and VDT constructs directly is required.

7.5.1 Limitations & future directions

Though the sample was deliberately selected for neuroticism score, to assess the role of neuroticism a full spectrum of neuroticism scores would add insight in to how the presented relationships work on a continuum of neuroticism. Future work should include those within the normal distribution of neuroticism as this would allow discussion of VDT constructs in a population of ‘normal’ personality traits, as well as assessment of this relationship on a continuum. Further, as the sample was selected for neuroticism level the results of this chapter must be taken with caution, as findings may have been

exaggerated by use of divergent neuroticism scores. There is also evidence that high-order personality traits have predictable relationships with each other (e.g. Tobin, Graziano, & Tobin, 2002) which raises the possibility of other traits being unintentionally affected by neuroticism selection. It would, however, be of interest to assess the potential role of agreeableness in interpersonal antagonism and extraversion in the impulsivity that also features in the VDT in the future. Replication of these findings across a multitude of VDT questionnaires is crucial, though by design there should be considerable parity across measures. Though in line with original power calculations with a large effect size, sample size is limited regarding the bivariate correlations and identification of moderate (or smaller) effect sizes. This analysis would therefore benefit from additional participants before strong conclusions can be drawn.

7.6 Conclusion

The experiment supports neuroticism as both a transdiagnostic risk-factor (Lahey, 2009) featuring in maladaptive personality as well as mood and anxiety disorders, but also as an elemental core of the VDT (Miller, Dir, et al., 2010). Neuroticism score was related to differences in expressed traits in the VDT constructs. Specifically, high neuroticism related to emotional instability in vulnerable narcissism, and interpersonal antagonism in secondary psychopathy. High neuroticism was related to expression of both these concepts in BPD traits, which could suggest malignancy of BPD relative to other constructs. Exploratory analysis hinted at the potential role of other overarching personality traits such as agreeableness and conscientiousness in VDT construct expression. Self-criticism was shown to have differential relationships across the VDT constructs in high vs. low neurotic individuals, though self-hatred was consistently associated with the VDT. Anxiety as a separator of primary and secondary psychopathy was not supporting in the present results, though limitations of this finding are discussed. As neuroticism doesn't explain full expression of construct characteristics, future work investigating the role of prosocial overarching personality traits in this relationship would be of interest given the characteristic interpersonal antagonism.

Chapter 8: General discussion

8.1 Aims

The aim of this thesis was to explore neuroticism as a transdiagnostic factor in generalized anxiety disorder (GAD) and major depressive disorder (MDD), and further to explore potential interactions between neuroticism and disorder specific dimensions within these diagnoses. Specifically, the role of neuroticism in defensive behaviours and negative self-reflection in healthy controls, GAD and MDD was explored, alongside analysis of neuroticism within vulnerable dark triad (VDT) characteristics. This thesis also had a focus on the development of related tools, including: 1) development of an online pre-screening tool using self-report neuroticism in recruitment to clinical trials; 2) piloting the Joystick Operated Runway Task (JORT; Perkins et al., 2013) measure of defensive behaviour for use in individuals with GAD in a pharmacological fMRI study for the first time; 3) applying the Fake IQ Test (FIQT), a novel adaptation of a pre-existing measure of perceptions of (own) performance (Nuttin & Greenwald, 1968), to a large adult psychiatric population.

8.2 Neuroticism as a transdiagnostic factor

The findings outlined in this thesis support neuroticism having a transdiagnostic association in GAD and MDD (Bienvenu & Stein, 2003; Clark et al., 1994; Cremers et al., 2010; Griffith et al., 2010; Kotov et al., 2010; Lahey, 2009; Sutin et al., 2010), as evidenced by consistently high neuroticism scores associated with presence of MDD, GAD or co-morbid history of both in the presented results. Further, study 1 in chapter 3 demonstrated robust sensitivity of self-report neuroticism in identification of individuals with a lifetime history of GAD or MDD; supportive of this, high neuroticism scores were associated with both GAD and co-morbid history of GAD and MDD in chapter 6. These findings are given ‘real-world’ context and support through the successful piloting of an online self-report neuroticism measure as a novel pre-screening tool in recruitment of individuals with GAD to a clinical trial, as described in chapter 3. Recruitment is one of the largest limiting factors in clinical trials (Borschmann et al., 2014; Kasenda et al., 2014; McDonald et al., 2006; Sullivan, 2004), due in part to the need for non-complex (often single-diagnosis) and treatment-free individuals (Wise et al., 2016) but

also as a result of the time-pressure researchers and gatekeepers are under (Sullivan, 2004; Wise et al., 2016). As such, the ability to use a non-invasive self-report measure that can be administered remotely with little input from researchers, such as demonstrated in chapter 3, could be beneficial to research. This is especially pertinent given the low cost involved in screening thousands of individuals remotely online.

Looking beyond mood and anxiety disorders, neuroticism has been posited as the ‘core’ of the VDT in the literature, based on the emotional instability, affective fluctuation and interpersonal antagonism characteristic of the triad (Jones & Figueredo, 2013; Miller, Dir, et al., 2010). The evidence presented in this thesis does partially support this role for neuroticism in the VDT: above average scores in the VDT constructs of vulnerable narcissism and secondary psychopathy were associated with high neuroticism. This relationship was not significant in borderline personality disorder traits (BPD), though this could be due to low power, as discussed in chapter 7; alternatively, previous work has also provided contradictory information regarding neuroticism levels in BPD (Clarkin et al., 1993; Miller, Dir, et al., 2010; Morey & Zanarini, 2000). Post-hoc analysis in chapter 7 hinted at a role for prosocial traits, such as agreeableness, in the VDT. This finding indicates that neuroticism is not the only ‘core’ of the VDT and supports suggestions in the literature that the VDT may consist largely of low agreeableness and high neuroticism (Miller, Dir, et al., 2010).

Though further exploration was beyond the immediate scope of this thesis, the presented findings indicate potential for neuroticism as factor in maladaptive personality more widely. Indeed, research has considered the role of neuroticism in the context of a spectrum model of narcissism, with high neuroticism linked to vulnerable narcissism and at the other end, low neuroticism associated with grandiose narcissism (Jauk et al., 2017; Krizan & Herlache, 2018), providing the theoretical framework for this suggestion. Following the successful pilot of the online self-report neuroticism tool for trial recruitment in chapter 3, a similar concept for identification of individuals with high VDT scores may also be possible. This is pertinent given the current paucity of research in the VDT and links between the constructs of the VDT and negative psychological and social outcomes (Annen et al., 2017; Dugal et al., 2018; Miller, Widiger, et al., 2010; Unterrainer et al., 2016).

8.3 Maladaptive neuroticism

Though long associated with pathology (Bagby & Rector, 1998; Bienvenu & Stein, 2003; Clark et al., 1994; Kendler, Kessler, Neale, Heath, & Eaves, 1993; Kendler, Kuhn, & Prescott, 2004; Khan, Jacobson, Gardner, Prescott, & Kendler, 2005; Kotov et al., 2010; Lahey, 2009; Navrady et al., 2017), the details of precisely how neuroticism relates to negative outcomes are unclear. This thesis outlines several examples of links between neuroticism and harmful cognitive and behavioural characteristics in GAD, MDD and co-morbid history of both disorders.

Previous work has suggested that neuroticism is linked to psychiatric comorbidity (Lahey, 2009), including co-morbidity between depression and anxiety disorders (Khan et al., 2005). Chapter 6 indicated significantly higher neuroticism scores in those with a co-morbid history of GAD and MDD, compared to those with MDD alone. If co-morbidity is taken as reflective of greater disease burden (Grant et al., 2005), these results could support a continuum model of neuroticism with increasing scores reflecting greater pathology. However, no difference between GAD and co-morbid history in neuroticism score was observed in chapter 6. This may reflect greater overlap between neuroticism and GAD; a large degree of overlap in measures of neuroticism and GAD has been noted (Hettema et al., 2004), supported by sensitivity analysis in study 1 of chapter 3 which indicated slightly better specificity for neuroticism in identification of GAD relative to MDD. Alternatively, the high levels of neuroticism in both GAD and co-morbid history might suggested that GAD has a greater burden than MDD. However, unipolar depression is considered a leading cause of disability-adjusted life years and burden (Ferrari et al., 2013; Murray & Lopez, 1997), and mood disorders such as depression are among the greatest risk factors for suicidal ideation (Nock et al., 2008). As such, it is unlikely that GAD is simply more severe than MDD. As the same sample was used in the sensitivity analysis in chapter 3 and in the analysis in chapter 6 further research is required before more definite conclusions can be drawn; direct comparison of the life-impact of GAD and MDD, and the role of neuroticism in disease burden and/or severity would be of interest. Indeed, there is evidence that other personality traits, such as openness to experience, are associated with symptom-level severity in conditions such as obsessive-compulsive disorder (Rector, Richter, & Bagby, 2005) and that neuroticism can contribute to poorer quality of life

in disorders such as Parkinson's disease (Dubayova et al., 2009), suggesting that there may be grounds to conceptualize neuroticism as linked to increased disease severity and burden. If supported by further research the findings presented here indicate that this could apply to severity of mood and anxiety disorders, which would support a transdiagnostic role for neuroticism in psychopathology.

Regression analysis in chapter 6 indicated that neuroticism score consistently predicted self-criticism across GAD and dual groups, a relationship that was affected by trait agreeableness scores. These results are potentially supportive of neuroticism as a moderator of disorder related characteristics (Claridge & Davis, 2001) as self-criticism is manifest in both GAD and MDD (Cox et al., 2001, 2000; Iancu et al., 2015; St. Germain & Hooley, 2012). The findings also support an understanding of neuroticism as a maladaptive factor in this context, as self-criticism is associated with increased risk of negative outcomes such as non-suicidal self-harm (St. Germain & Hooley, 2012). The effect of high neuroticism on self-criticism was slightly reduced by extraversion. Though conscientiousness is usually considered protective (Ode & Robinson, 2007; Turiano, Mroczek, Moynihan, & Chapman, 2013; Weston & Jackson, 2015), alongside agreeableness it was associated with a slight increase in the strength of the relationship between neuroticism and self-criticism. This was unexpected, though there is evidence to suggest prosocial traits such as agreeableness are associated with submission to others (McCrae & Costa, 1989) which is maladaptive defensive mechanism resulting in dismissal of own needs potentially leading to more negative self-reflection (Gilbert & Procter, 2006). Though the additional variance explained by these traits was small, this is indicative of additional personality traits as risk factors in mood and anxiety disorders. Like neuroticism, agreeableness, extraversion and conscientiousness are all easy to administer, non-invasive, self-report measures; as such, these would be simple additions to a screening routine using neuroticism to help identify those particularly at risk of anxiety and mood disorders.

Neuroticism was also related to differential expression across the three constructs of the VDT. The level of neuroticism had a stronger effect in emotional stability and self-concern in vulnerable narcissism, but in secondary psychopathy was more involved in interpersonal issues. In something of a double dissociation, neuroticism was not particularly related to interpersonal antagonism in vulnerable

narcissism, nor emotional instability in secondary psychopathy, despite the same individuals answering the both questionnaires. BPD meanwhile was highly affected by neuroticism score across both interpersonal antagonism and emotional instability, suggesting particularly strong relationship. This is interesting, as a significant difference in BPD score was not shown between the high and low neuroticism groups in chapter 7 (as outlined above). As vulnerable narcissism is characterised by self-interest and emotional instability (Annen et al., 2017) and secondary psychopathy by abnormal social and interpersonal behaviour (Miller, Dir, et al., 2010), it appears that neuroticism may enhance negative co-existing features and temperamental characteristics of the individual, leading to specific symptomology. This is in line with previous work suggesting neuroticism moderates psychopathological expression by intensifying the individual's existing characteristics leading to maladaptive behaviours, reflecting different conditions (Claridge & Davis, 2001). This again indicates the malignancy of neuroticism at high levels, as emotional instability, interpersonal antagonism and the VDT constructs are associated with increased psychosocial dysfunction and negative outcomes (Dugal et al., 2018; Feske et al., 2006; Miller, Dir, et al., 2010; Neria et al., 2016; Unterrainer et al., 2016).

Some of the relationships between the VDT constructs and self-criticism also appears to depend on neuroticism level. For example, vulnerable narcissism only correlated with the toxic attitudes of self-hatred and self-inadequacy when individuals also had high levels of neuroticism; secondary psychopathy also only had a relationship with self-hatred in those with high levels of neuroticism, whilst BPD was only related to self-inadequacy under the same conditions. It may be that, as suggested by Claridge & Davis (2001), neuroticism is associated with or leads to malevolent expression of disorder-relevant characteristics. As shown in chapter 7 there are individuals who show high scores on the VDT constructs without high neuroticism, though the low-neuroticism group do not show a significant relationship to measures of self-critical attitude. These findings are supportive of the concept of neuroticism as a moderator, though potentially reduce the argument for neuroticism as the 'core' of the VDT (at least, in isolation). However full conclusions cannot be drawn as the individuals in chapter 7 were selected for neuroticism score (high or low, measured as 1 standard deviation above or below the population mean defined in chapter 3), meaning there was no continuum of scores or an average

neuroticism-scoring group to further test this hypothesis against. This experimental design choice also limits discussion of agreeableness as an alternate or additional ‘core’ to the VDT, as discussed above and in chapter 7.

8.4 Is there such a thing as adaptive neuroticism?

The relationship between self-reassurance and neuroticism diverged between healthy and groups with self-reported MDD, GAD or co-morbid history of both. Higher neuroticism was related to higher levels of self-reassurance in the healthy control group; conversely, raised neuroticism was linked to poorer ability to self-reassure in those with MDD, GAD or co-morbid history of both. It may be that at ‘healthy’ levels neuroticism can have a positive effect on self-compassionate cognition. As neuroticism was positively related to self-criticism across psychopathology and health, the relationship between neuroticism and self-reassurance in healthy controls is an unusual finding. Positive associations of neuroticism are not common in the literature, which largely focuses on the vulnerabilities associated with this trait. The concept of ‘healthy’ neuroticism suggests that the characteristic worry and rumination of this trait can result in vigilance about personal health and health risk exposure that can be protective for health (Friedman, 2000). However, this notion usually involves simultaneously high conscientiousness and has exclusively focused on physical health to date (Friedman, 2000; Turiano et al., 2013; Weston & Jackson, 2015), indicating that these results represent a novel finding.

Previous work has emphasized the role of poor self-compassion and self-reassurance in conditions such as Social Anxiety Disorder (SAD; Werner et al., 2012) and the importance of self-reassurance in therapeutic approaches with a focus on compassion (e.g. Gilbert, 2009; Gilbert & Proctor, 2009). The GAD sample presented here had higher self-reassurance scores than the MDD group, suggesting that MDD may require additional input in self-compassionate behaviour. There is little work exploring healthy forms of rumination and worry in the literature, it would be beneficial to investigate this avenue and how neuroticism moves from a potentially adaptive to a maladaptive behaviour.

8.5 A multi-level approach: looking beyond neuroticism in mood and anxiety disorders

8.5.1 Negative self-reflection

As shown here and in the wider literature, neuroticism has poor specificity in mood and anxiety disorders (Claridge & Davis, 2001; Kotov et al., 2010; Lahey, 2009; Ormel et al., 2004). Therefore, differentiation between MDD, GAD and co-morbid experience of both disorders was explored based on forms of negative self-reflection.

Some level of separation of GAD and MDD based on perception of performance as measured by the FIQT was observed in chapter 6. Specifically, (self to) peer-comparison scores on the FIQT were raised in MDD and co-morbid history of both MDD and GAD, but not in single diagnosis GAD. Depression is thought to generate a global negative view of the self and the wider world (Beck, 1967), whereas there is some suggestion that anxiety may require more ego-involvement in provocation of self-criticism (Flett et al., 1995). As such, negative self-reflective attitudes in MDD may extend to situations with low ego-involvement (such as the FIQT), whilst the same does not appear true for GAD. Future research should explore this concept further, with comparison of low-ego involved tasks (like the FIQT) and paradigms with greater ego-involvement, perhaps using academic achievement. Further differentiation was indicated in chapter 6, as the self-hatred subscale of a self-criticism questionnaire was raised in those with a co-morbid history of both GAD and MDD, relative to single diagnosis of either condition and healthy controls. Notably, the MDD group also had significantly higher self-hatred scores than the healthy controls, though the GAD sample did not.

Taken together, these findings indicate the negative associations of MDD and co-morbidity, as evidenced by more globalised negative self-reflection and poorer ability to self-reassure. These findings also reflect the importance of looking beyond neuroticism: as discussed above, though the GAD group had higher neuroticism scores than the individuals reporting MDD, the self-criticism scores of the MDD group were more maladaptive. These findings provide interesting points of differentiation between the disorders (and co-morbidity), which could impact treatment approaches. If negative self-criticism in GAD is indeed restricted to the self, psychological intervention might beneficially focus on this process.

Similarly, approaches centring on building self-compassion may be particularly relevant to those with co-morbid MDD and GAD or pure MDD, due to the demonstrated raised self-hatred in these groups. As discussed in chapter 6, self-compassion and self-reassurance are important aspects of certain treatment approaches (Gilbert, 2000; Gilbert & Procter, 2006), indicating relevance to individualised care in these conditions.

8.5.2 *Defensive behaviours*

A further key aim of this thesis was to explore the relationship between neuroticism and active defensive behaviour. Unfortunately, inclusion of self-report measures of neuroticism in the defensive behaviour experiments was rare, so a comprehensive overview was not possible in the systematic review in chapter 4. However, a small number of studies did include measure of individual differences, providing some evidence that neuroticism and trait anxiety are linked to amygdala and cingulate cortex activation in response to threat (Cunningham et al., 2011; Mobbs, Petrovic, et al., 2009). Amygdala activation during emotional conflict has previously been linked to neuroticism (Haas, Omura, Constable, & Canli, 2007); indeed, the neural circuitry associated with neuroticism and emotional disorders overlaps greatly (Cremers et al., 2010; Hilbert et al., 2014; Nestler et al., 2002). The amygdala has been identified as an area involved in both top-down and bottom-up generation of negative emotion (Ochsner et al., 2016). It has been suggested that neuroticism is associated with the individual's perception of distance from threat (McNaughton & Corr, 2004), implying a role for neuroticism in maladaptive perception and inappropriate threat reactions.

The overlap of neuroticism, bottom-up and top-down processes in this region is curious. A change between prefrontal to midbrain processing as distance from threat reduced was shown in chapter 4, a finding which is discussed in the chapter as possibly representing a change from top-down to bottom-up processing in the face of more proximal threat. As such, it would be of interest to examine whether neuroticism plays a role in the point at which a switch between top-down and bottom-up occurs, potentially within the amygdala. It is conceivable that neuroticism may alter sensitivity to threat, resulting in earlier switching between these processes and possibly a quicker reliance on instinctive bottom-up impulsive processing during exposure to threat. This links with the association between

neuroticism and anxiety particularly (Griffith et al., 2010; Lahey, 2009) and provides conceptual support for neuroticism as an important for defensive behaviour. However, as so few studies identified in chapter 4 included neuroticism it is not possible to draw a strong conclusion currently. If supported with further research this finding could inform treatment, with a focus on altering sensitivity to threat or on bottom-up processes in those with higher levels of neuroticism.

More broadly, the importance of individual differences in defensive behaviours was highlighted by the finding in chapter 5 that individual's fear proneness was linked the behavioural effects of benzodiazepine administration. In this group of highly neurotic individuals, benzodiazepine administration was shown to increase flight intensity during avoidance of threat in those with low fear-proneness, but to decrease it in those with high fear-proneness. Though it should be noted that the fear-proneness scores of the present sample are likely higher than average due to selection of participants for high neuroticism scores, these findings are in line with previous work utilising the JORT (Perkins et al., 2013) and rodent models (Blanchard & Blanchard, 2008). This finding has clear clinical implications, as benzodiazepines may be contraindicated when administered to individuals with low trait fear-proneness. A role for trait characteristics in response to medication has been shown elsewhere (e.g. Glue, Wilson, Coupland, Ball, & Nutt, 1995). These results also reaffirm the importance of considering factors beyond neuroticism, as this finding was identified in a group of individuals already selected for high levels of neuroticism.

8.5.2.1 Neural networks in defensive behaviours

The review in chapter 4 broadly supported the neural predictions of Reinforcement Sensitivity Theory (RST) (McNaughton & Corr, 2004). Namely, a move from forebrain-to-midbrain activation in simple avoidance as threat becomes more proximal was observed. These findings are also largely in agreement with the literature surrounding neural activation and anxiety in humans (Bishop, 2007; Duval, Javanbakht, & Liberzon, 2015) and animals (e.g. see Blanchard, 2017 for a review). The findings support the involvement of innate bottom-up processing in situations requiring fast response to imminent threat, and high-order processing in situations where threat is more distal and evaluative responses can be made. Previous work has identified separable neural streams involved in top-down

and bottom-up processing: bottom-up emotion generation is linked to the bilateral amygdala, occipital cortex and right prefrontal and parietal regions, whilst top-down emotion generation was associated with the left prefrontal, cingulate, temporal regions, and the left amygdala (Ochsner et al., 2016). These areas are somewhat in line with the findings outlined in chapter 4 for simple avoidance and goal-conflict respectively. For example, the parietal lobule (Mobbs, Petrovic, et al., 2009) and bilateral amygdala (Rigoli et al., 2012) were identified in proximal threat, though the bi-laterality of amygdala activation was not consistent (Mobbs et al., 2007; Mobbs, Petrovic, et al., 2009). This partially supports the suggestion of a switch from top-down processing associated with decision making, to bottom-up processing as threat approaches.

Chapter 4 also suggests hippocampal involvement maintains involvement in approach behaviours under conflict when degree of spatial orientation required by the paradigm was considered, which was not the case in simple avoidance. In line with the predictions of RST (McNaughton & Corr, 2004), this novel finding supports a distinct role for the hippocampus in goal-conflict beyond simple avoidance and indicates the care that must be taken in paradigm design. Future directions for human defensive behaviour paradigm design is highlighted in the pooled-data analysis of chapter 4, which discusses the high heterogeneity in current tools. Though heterogeneity can be aid identification of robust regions of activation (Costafreda, 2009) the level shown in the review made direct comparison of data and results complex. Further, around half of the studies included in the meta-analysis had identified the subcortical high-threat related regions (PAG and midbrain particularly) using region of interest (ROI) analysis. Notably, how the PAG region identified in Mobbs et al was defined is not reported (Mobbs et al., 2007; Mobbs, Petrovic, et al., 2009). Given the limitations of ROI analysis, chapter 4 indicates a need to ensure robust analysis approaches to prevent confirmation bias.

Chapter 5 explored defensive behaviours in a group of individuals high in neuroticism who also had GAD. As such, the results discussed in chapter 5 were interpreted against the results of chapter 4 to consider how neuroticism is related to neural response during defensive behaviours. Previous work has either not included a measure of neuroticism or has used stimuli that are not directly comparable to fear states (e.g. emotional faces; Cremers et al., 2010). Chapter 5 was also novel in that the sample all met

the criteria for GAD as defined by the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998); as shown in chapter 4 no other behavioural explorations of neural activation in human defensive behaviour have recruited clinically anxious samples. Unexpectedly, the findings outlined in chapter 5 did not directly reflect chapter 4 or the wider literature. Despite being core features of the systematic review in chapter 4, a forebrain-to-midbrain change in line with threat proximity was not observed in chapter 5, nor was hippocampal activation shown in goal-conflicting situations. This may have been due to paradigm oversights, as discussed in the tool development section below. Further, as only individuals with high neuroticism were enrolled a comparison with activation in individuals with average (or low) levels of neuroticism was not possible, which limits the understanding it is possible to draw from this analysis.

8.6 The anterior insula as part of a neural network for neuroticism in anxiety and mood disorders?

Though chapter 5 did not fully replicate the findings of chapter 4, it did identify hyperactivation of the anterior insula in avoidance of threat during flight (across trial types), which was also present in the systematic review. Altered activation of the insula has been proposed by some as a potential neuroanatomical candidate for anxiety sensitivity (Paulus & Stein, 2006). Research has highlighted anterior insula involvement across a range of anxiety diagnoses (Shin & Liberzon, 2010), including social phobia (Lorberbaum et al., 2004) and simple phobia (Paulus & Stein, 2006; Rauch et al., 1997; Wendt, Lotze, Weike, Hosten, & Hamm, 2008) with some evidence suggesting normalisation of insula activation after successful treatment in the latter (Goossens, Sunaert, Peeters, Griez, & Schruers, 2007). Aberrant activation and connectivity of the anterior insula has also been associated with MDD (Horn et al., 2010; Mayberg, 2003) and high neuroticism (Feinstein, Stein, & Paulus, 2006; Paulus et al., 2003; Stein et al., 2007). Atypical activation of the anterior insula could represent a neurobiological candidate associated with depression as well as diverse anxiety diagnoses, potentially arising from transdiagnostic neuroticism.

The anterior insula is responsible for interoceptive experience (i.e. behavioural and emotional processes associated with physiological status of the body; Domschke, Stevens, Pfleiderer, & Gerlach, 2010;

Paulus & Stein, 2006), with evidence linking this region to processing of pain and bodily sensation (Kirlic et al., 2017; Talmi et al., 2009) and the integration of external threat with internal perceptions (Paulus & Stein, 2006). Abnormal interoceptive processing is posited as an important aspect of anxiety disorders (Olatunji, Deacon, Abramowitz, & Valentiner, 2007; Paulus & Stein, 2006); further, the somatic symptoms associated with MDD have been tied to abnormal interoceptive representation in the anterior insula (Avery et al., 2014). Neuroticism too has been linked to somatic symptom reporting (Parker, Bagby, & Taylor, 1989). The anterior insula also has connections to the amygdala (Phelps et al., 2001) and the wider limbic system (Horn et al., 2010); these areas are not only associated with fear (Kirlic et al., 2017; McNaughton & Corr, 2004) but with interoceptive processes (Domschke et al., 2010) and are also key in anxiety disorders, MDD and neuroticism (Cremers et al., 2010; Hilbert et al., 2014; Keightley et al., 2003; Nestler et al., 2002; Opel et al., 2018; Sutin et al., 2010). This evidence supports a crucial role for the anterior insula in GAD and potentially MDD also, though future work should explore whether this network is mediated by neuroticism level. It should be noted that the sample in chapter 5 had both high neuroticism and GAD, and as such may be expected to show abnormal insula activation based on either of those qualifiers. As such future work with a wider spectrum of neuroticism is key. These findings should be considered within the context of the wider shared neural network between neuroticism and mood and anxiety disorders, which largely focuses on the amygdala, anterior cingulate cortex, limbic-frontal circuitry and prefrontal regions (Beesdo-Baum et al., 2011; Cremers et al., 2010; Hilbert et al., 2014; Keightley et al., 2003; Sutin et al., 2010); these networks and their relationships with the anterior insula are discussed in more detail in chapters 4 and 5.

8.7 A general neurotic syndrome?

The DSM approach to psychiatric diagnosis has been criticised not only for its highly categorical style but also for its poor ability to represent a longitudinal understanding of mental health, particularly in mood disorders (Fava, 1999; Tyrer, Tyrer, & Guo, 2016). Several authors have highlighted the presence of changeable levels of experienced depression and anxiety (which at times are at subthreshold levels) accompanied by specific anxiety symptoms (i.e. obsessive-compulsive, social phobic and agoraphobic) and co-morbid personality dysfunction (Reich & Thompson, 1987; Tyrer et al., 2016) through the

lifespan in a subgroup of individuals with depression and anxiety disorders; crucially, the presence of these features fluctuates in line with life events (Tyrer, Seivewright, Ferguson, & Tyrer, 1992; Tyrer, 1985; Tyrer et al., 2016). In response to these observations, a new diagnostic label of general neurotic syndrome was coined, defined as: “a persistent or relapsing disorder of combined anxiety and depressive symptoms...associated with anxious, dependent and obsessional personality dysfunction, often interspersed with episodes of social anxiety, panic and somatoform symptoms” (Tyrer et al., 2016, p 193).

Though this thesis does not have a longitudinal approach the consistent involvement of neuroticism in MDD, GAD and co-morbid history of both is broadly supportive of an overarching dimensional approach to these disorders, with a role of persistent personality characteristics. The authors of the general neurotic syndrome scale propose that including both personality and (fluctuating) clinical manifestation provides a more in depth understanding of the individual and their treatment needs, as well as enabling awareness of stable factors that may impact prognosis (i.e. personality traits) (Tyrer et al., 2016). This supposition is supported by evidence that disordered personality is associated with greater persistence of anxiety disorders (Skodol, Geier, Grant, & Hasin, 2014) and findings suggesting that individuals with general neurotic syndrome have higher rates of relapse and poorer psychosocial outcomes relative to individuals with a diagnosis of depression or anxiety alone (Tyrer et al., 1992).

The work presented in this thesis supports the concept of assessing personality traits and characteristics alongside clinical symptoms, as indicated by the altered relationship between neuroticism and self-criticism across mood and anxiety disorders. Further, the presence of greater neuroticism scores and raised self-hatred in individuals with co-morbid history of GAD and MDD compared to those with a single diagnosis of either is in line with identified poorer outcomes for those with general neurotic syndrome. This is not to suggest that all individuals with MDD or GAD are instead experiencing general neurotic syndrome, but rather that a subgroup of individuals with particular risk factors, outcomes and needs might be identified through attention to concurrent temperamental and personality characteristics. Though not currently represented in the DSM, arguments for its inclusion have been proposed (Peter Tyrer et al., 2016). Given the identification of the anterior insula as key in MDD, GAD and neuroticism

exploration of neural activity in this region in individuals on the spectrum of general neurotic syndrome would be an informative next step, especially should it appear in future version of the DSM.

8.8 Tool development

An additional aim of this thesis was to develop and pilot three tools. The relative success of these pilots and future considerations are outlined below.

8.8.1 Pre-screening clinical trial volunteers using an online measure of neuroticism

Neuroticism was shown to have good predictive ability for the identification of individuals meeting the criteria for GAD in chapter 3. The online tool enabled successful recruitment of a full study population within the challenging timeline required. This method combines the cost and time efficiency of online advertisement of research studies (e.g. Wise et al., 2016) with use of a non-invasive self-report measure with robust links to the study population. This is in line with current initiatives around the use of digital technology in research (Department of Health and Social Care, 2017) and additionally may allow recruitment across wider population pools than is achieved by traditional methods. Though the tool was successfully applied here, future research should explore a direct cost comparison with traditional methods of recruitment and might further assess the rate of false positives against recruitment through clinical services, which was not possible in this project. Neuroticism was also shown to have strong predictive ability for having had a diagnosis of MDD with a reasonable degree of specificity (shown in chapter 3), suggesting this tool may have immediate applicability beyond GAD.

Utilising the findings of this thesis, a refined version of this might be proposed. Under this approach neuroticism would be measured in individuals first, before assessing individual differences in negative self-reflection and defensive behaviour, forming a two-tiered approach. Other big-5 traits might also be included, given the association between agreeableness and conscientiousness scores and increased strength of the relationship between neuroticism and self-criticism shown in chapter 6. The concept of a two-tiered approach, potentially with overarching neuroticism as the key facet, is supported by other reports in the literature (Barlow et al., 2014; Caspi & Moffitt, 2018). This approach would allow for non-invasive identification of individuals potentially meeting the criteria for MDD or GAD, but who

are not currently in touch with clinical services. This would be beneficial to early-stage clinical trials particularly.

8.8.2 *The Joystick Operated Runway Task (JORT)*

Chapter 5 piloted the JORT in a sample of individuals with GAD. The results indicated no difference in neural activation after anxiolytic administration, or between trials (simple avoidance vs. goal conflict). Several conclusions about the current JORT paradigm can be drawn. Most fundamentally, the two arms (simple avoidance and goal-conflict) in the JORT may not accurately reflect these behaviours. Specifically, the goal-conflict arm was designed to represent the risk-assessment behaviour demonstrated by rats when in conflicting situations (Blanchard & Meyza, 2017; Perkins et al., 2013), representing anxiety in RST (McNaughton & Corr, 2004). The results in chapter 5 suggest there was actually little difference between this and the simple avoidance (flight) trials, and that the trials arms may instead reflect two types of active avoidance (one simple and one requiring more motor complexity). As the goal-conflict arm currently offers no benefit from approaching the top red dot (beyond necessity, to avoid the bottom red dot), it is unlikely this is tapping true risk-assessment behaviour (see Figure 9 in chapter 5 for a diagram of the current JORT set up). An improvement to the JORT in this respect would be to create a more incentivised approach mechanism, where information is gained through approach. For example, whether the top dot is dangerous or not could be hidden until the participant approaches it (possibly by the top dot showing in grey until it is approached, where it can turn red or green to signal danger or safety respectively), an approach used by others in the literature (Rigoli et al., 2012). Alternatively, a reward system could be implicated, where individuals can receive a pleasant outcome if they get close enough to a potential danger without being ‘caught’ (mimicking cautious approach). Typically, paradigms using reward incentives use monetary or point-based gain (for example, Aupperle et al., 2015; Bach et al., 2014; Gonen et al., 2016); as discussed in chapter 4, this could be problematic when used in combination with threats that are immediately received (such as the electric shocks used in the JORT currently). As such, an exploration of immediate rewards would be wise before this approach is taken.

Potential developments of the JORT are also highlighted by the systematic review of human defensive behaviour paradigms in chapter 4. Very few studies include a freeze or a fight option in simple avoidance of threat, despite purporting to address the fight-flight-freeze system. A useful addition to the JORT would be to include freezing and fighting options, to capture these integral aspects of threat avoidant behaviour (McNaughton & Corr, 2004). This could be achieved by attributing interactive response abilities to the red dots, in which freezing might ‘hide’ the participant (green dot) for a period and fast approach might ‘scared off’ the red dots. This also lends itself to tasks with a maze set up (e.g. Mobbs et al., 2007, 2009) or in open-field type tasks (Collins et al., 2014).

Most crucially, uncertainty is considered integral to the experience of anxiety (Jackson, 2009). Currently, the JORT involves no uncertainty: it is dependent only on skill, as if the participant gets caught and there is a shock symbol on screen, they will receive a shock. This omission may partially explain the lack of difference in neural activation between simple avoidance (i.e. fear) and goal-conflict (i.e. anxiety) trials, which is in contradiction with key theories (McNaughton & Corr, 2004). Adding an element of uncertainty to JORT outcomes would be a significant improvement. This could take the form of a hidden predator (as in Rigoli, Ewbank, Dalgleish, & Calder, 2016), not revealing whether trials are active (you will receive a shock) or inactive (you will not), or alternatively through the use of probabilistic capture in which the tool is programmed to only allow escape in a predetermined number of trials (e.g. Montoya, van Honk, Bos, & Terburg, 2015; Schlund et al., 2016; Wendt, Löw, Weymar, Lotze, & Hamm, 2017).

As an aside, the importance of using active paradigms in human defensive behaviour is worth considering. The review presented in this thesis was focused on active behavioural tools, rather than self-report. Imaginative states involve top-down processing and may require increased involvement of prefrontal regions (Buckner & Carroll, 2007), suggesting that self-report type measures of defensive behaviour may overly bias activation to these regions. Neural areas identified in chapter 4 did overlap to some degree with those identified in a review of imagined mental state using threat-script experiments (Shuhama et al., 2017), which required participants to use imaginative states. Frontal and subcortical activation was present in both reviews, including preferential activation of subcortical regions during

processing of imminent threat. However, only one of the mental imagery experiments identified the midbrain regions and the authors reported that it wasn't possible to observe the entire defensive cascade (Shuhama et al., 2017). Comparatively, midbrain, insula and PAG activation during imminent threat exposure was a robust finding in the systematic review presented in chapter 4. Following, there is a potential flaw in reliance on subjective imaginative states of fear in exploration of human defensive behaviours. Evidence suggests that threat presence can elicit defensive responses without conscious subjective experience of fear (LeDoux et al., 2017) and that subjective fear does not necessarily influence biological response (Etherton, Lawson, & Graham, 2014). Further, there is an argument that mental imagery more accurately reflects strategy choice, rather than actual behaviour (Shuhama et al., 2017). This makes direct comparison of subjective and objective experience of fear complicated. Bottom-up processing may not be as effectively triggered by imagined mental states, which may instead result in greater reliance on frontal regions and top-down processing (Buckner & Carroll, 2007).

8.8.3 *The Fake IQ Test (FIQT)*

As outlined in chapter 6, the FIQT was developed from Nuttin and Greenwald's (1968) original measure. The version explored in this thesis (the FIQT) differed from the original in several meaningful ways. Key changes include the removal of any external feedback on performance and alteration of the questions asked after each trial. The in the FIQT questions were rephrased in order to tap comparative self-reflection, as an addition to self-satisfaction which was explored in the original. Negative comparison of self- to others is thought to have a stronger relationship to psychological distress than internalized self-criticism (i.e. comparison of self to internalized standards) (Hermanto et al., 2016), suggesting that this question may have a relationship with presence of psychopathology. The final question, regarding importance of performance on the task, was introduced to assess whether individuals with psychopathological functioning placed more importance on 'trivial' task performance, potentially representing overgeneralized perfectionism. It was expected that the FIQT would provide results related to self-criticism scores. However, as shown in chapter 6 the FIQT was not reliably related to a well-validated self-report measure of self-criticism. As discussed above, this could mean the FIQT

and perception of performance is a distinct aspect of self-reflection, or perhaps that there is a difference between ego-centric self-criticism and broader self-critical attitude that extends to the outside world.

The FIQT was used in conjunction with the Forms of Self-Criticising/attacking and Self-Reassuring Scale (FSCSRS; Gilbert, Clarke, Hempel, Miles, & Irons, 2004), which asks questions with a high level of ego-involvement (e.g. “I still like being me” and “I am easily disappointed with myself”). To fully gauge whether the FIQT (peer-comparison arm) does provide differentiation between GAD and MDD due to ego-involvement, comparison of the FIQT with a range of measures of self-criticism and measures of ego-centricity, such as the Egocentricity Index (Hart, 1991), is necessary. Self-criticism has been shown to relate to important clinical considerations such as treatment response (Blatt, 1995; Hermanto et al., 2016) and risk of co-morbidity (Kopala-Sibley et al., 2015). It would be beneficial to establish whether the FIQT is also related to these outcomes, though initial findings suggest no relationship between the FIQT and response to therapeutic intervention in depression (Marwood, 2017). The present findings indicated little consistency in the relationship between the FIQT and self-criticism outside of healthy controls; a potential avenue for future research is comparison between the FIQT and measures of perfectionism. Perfectionism has links to self-evaluation of performance (Stoeber et al., 2008), and has been proposed by some as another transdiagnostic risk factor for mood and anxiety disorders (Egan et al., 2011). As such, it would be interesting to also explore neuroticism in the context of perfectionism and the FIQT.

In line with the overall aim of this thesis, the FIQT may tap a mechanism that presents differently between MDD and GAD, and as such could provide a non-invasive method of assessing presence of these disorders with relevance to certain groups who have less insight (e.g. very young children, Autism spectrum disorders) and different methodologies such as MRI, as the FIQT does not require imaginative states which can be problematic in these settings (Klein & Gangi, 2010). However, further exploration of the tool and its association with wider psychological concepts, such as perfectionism, is required before the utility of the FIQT is understood.

8.9 Limitations & methodological considerations

The majority of work presented in this thesis benefits from large and well powered samples. Chapter 5 involved within-subject controls for individual differences in brain structure, and additionally was controlled with both placebo and an alternate anxiolytic. Both the JORT and FIQT are designed to avoid the major self-report issue of reliance on imaginative state, as touched on in chapter 6 and above. The FIQT was assessed as a potential measure of self-criticism by direct comparison with a very well validated measure (Gilbert et al., 2004). Chapter 5 measured active defensive behaviour in individuals with GAD for the first time in a sample with minimal co-morbidity, giving reliable insight in to defensive behaviour in this disorder specifically.

There are limitations to the work in this thesis, particularly due to recruitment and sampling choices. Chapter 5 involved recruitment of individuals with GAD and high neuroticism scores, but no control group (regarding neuroticism or GAD) was included. The within-subject repeated-measures placebo-controlled design did allow individuals to serve as their own control, which can be a boon in neuroimaging due to the infinite individual variation in brain structure. However, inclusion of a non-anxious control group would have added depth and certainty to the conclusions drawn from this chapter. Importantly, without a low neuroticism scoring group, it is difficult to be definitive that the results are specific to high neuroticism. Similarly, chapter 7 recruited individuals based on their neuroticism score (one standard deviation above or below the population average as defined in chapter 3). This approach was used to maximise hypothesis testing ability under time pressure, but inclusion of middle-range neuroticism scorers would have added breadth to the result and conclusions drawn. These chapters form initial explorations of neuroticism and behaviour, but wider populations and samples will be required in future research.

As is often the case in psychological research, the data sets involved in this thesis frequently had large gender skews. This is particularly true of chapter 5. As the sample was majority female, this does limit the degree to which conclusions can be drawn about males from the results presented. However, where appropriate and/or possible, gender was controlled for in analysis and was then not found to significantly affect results. Further, there is generally a bias towards women in development and

diagnosis of (e.g.) anxiety disorders (McLean, Asnaani, Litz, & Hofmann, 2011). Regardless, the gender bias in the available data may limit wider generalisation.

8.10 Future directions

In addition to the suggestions already covered in this chapter, there are several key future directions for this research. Firstly, the present work only explores neuroticism in GAD, MDD and the VDT. A major future direction for this work is to broaden to additional diagnoses and psychopathologies. A wide range of pathologies are associated with high neuroticism, such as somatoform disorders, panic disorders, substance abuse disorders and eating disorders (Khan et al., 2005; Lahey, 2009; Malouff et al., 2005). Exploring the ability to use a tool such as our self-report measure of neuroticism as an online screening procedure for recruitment of individuals not currently in contact with clinical services in a non-invasive manner would be a logical first step.

This future aim is applicable to defensive behaviours too, as a range of disorders including OCD and autism (Gillan et al., 2014; Servatius, 2016) are thought to be feature maladaptive defensive behaviour. Depression is a key disorder associated with dysfunction in defensive behaviour (Bijttebier et al., 2009; McNaughton & Corr, 2004); initial exploration in depressed samples using the JORT has not found differences in behavioural or neural activation (Marwood, 2017), though following the changes to the JORT suggested above it would be worth re-exploring this avenue. Further, vigilance to threat and behavioural inhibition may be hyperactive in vulnerable narcissism (Krizan & Herlache, 2018), whereas grandiose narcissism has links to increased approach behaviour in conflicting situations (Foster & Trimm IV, 2008). Vulnerable and grandiose narcissism are parts of the VDT and dark triad (DT) respectively, suggesting that the JORT or JORT-type measures could provide insight in to variation between these related personality styles, which some suggest are part of a continuum (Miller, Dir, et al., 2010).

The role of neuroticism in negative self-reflection has relevance to diagnoses such as anorexia or bulimia with their close links to self-criticism (Dunkley & Grilo, 2007) or on the other end of the spectrum, conditions with an inflated ego such as grandiose narcissism (Pincus & Lukowitsky, 2010).

Indeed, chapter 7 forms the basis of this idea, through analysis of vulnerable narcissism. It would also be of interest to explore the FIQT in the context of diminished self-reflection, as though the precise nature of this measure of self-reflection is not yet clear, ego-centricity appears relevant. Exploration in individuals with high levels of primary psychopathy or those on the Autism spectrum could provide insight, due to typically lower self-reflection in these conditions (Philippi & Koenigs, 2014).

Chapter 4 highlighted the presence of a change in neural activation from the forebrain to midbrain. Unfortunately, few of the studies included in chapter 4 explored neuroticism in the context of defensive behaviours, but it would be of great interest to see whether neuroticism maps on to perception of threat distance and the speed of these changes, in line with models of defensive distance and RST proposals (McNaughton & Corr, 2004). This has applicability to specific disorders such as OCD, due to altered estimation of threat in this condition (Rector et al., 2005), similar to that though to be present in high neuroticism (McNaughton & Corr, 2004). Further, direct comparison of healthy controls and individuals with anxiety disorders on active measures of human defensive behaviour is a vital next move.

Descriptions of causality are beyond the scope of this thesis, due to the data collection and methodology approach used. However, longitudinal studies suggest that neuroticism does precede the onset of MDD and anxiety disorders (Clark et al., 1994; Ormel et al., 2004); exploration of variation in self-criticism and defensive behaviour would be useful in developing accurate screening tools for mood and anxiety disorders. There are several theories regarding the precise nature of the relationship between personality and psychopathology. For example, some models propose a common cause of both personality and disorder, others hold personality as a precursor (or subclinical version of) pathology or maintain personality has a pathoplastic relationship with diagnoses, or even suggest that personality is a product of experienced mental health atypicality (Gotlib & Hammen, 2008). Establishing the chronology and causality behind personality and pathology is of high importance.

8.10.1 Adopting a transdiagnostic neuroticism approach to mood and anxiety disorders

A transdiagnostic approach to mood and anxiety disorders has benefits for clinical screening for psychopathology, but also for research. A transdiagnostic approach would measure neuroticism in individuals initially, followed by an assessment of individual differences in negative self-reflection and defensive behaviour. This would form a two-tiered approach, allowing more nuanced understanding of the behavioural and cognitive symptom profiles in individuals and disorders. For example, according to data presented here raised self-hatred may be indicative of greater risk of co-morbidity, whereas more negative comparison of self- to- other on the FIQT could reflect MDD tendencies rather than GAD, which potentially requires greater ego-involvement before negative comparisons arise. This is similar to proposals by Barlow and colleagues (2014) and Caspi & Moffitt (2018), but with novel lower-tier factors proposed in line with the findings presented in this thesis.

These measures are all low-invasive, simple self-report questions which could be administered remotely online, reaching large numbers of individuals. As such, an approach such as this would be a potentially cost- and time- effective method of screening for individuals at risk of psychopathology. As indicated in this thesis, further big-5 traits such as conscientiousness, agreeableness and extraversion may have an impact on maladaptive neuroticism: these would also be easy to add to a screening battery. Further, the findings presented in this thesis suggest that characteristics such as self-criticism, agreeableness and conscientiousness are factors of interest to understanding mental health and risk of psychopathology: the UK Biobank, a nation-wide resource with a focus on prevention, diagnosis and treatment of a range of physical and mental health disorders, currently collects data on neuroticism but little comprehensive information about other factors such as these. The results of this thesis support importance of gathering data on transdiagnostic factors such as neuroticism, but also indicate the value in observing lower-level disorder-specific factors such as (negative) self-reflection.

8.11 Overall conclusions

The primary aim of this thesis was to explore neuroticism as a transdiagnostic factor in GAD and MDD. Raised neuroticism was present in both disorders throughout this thesis, and further was successfully

employed as a low-impact and method of identifying treatment-free individuals with GAD for enrolment in a phase II clinical trial. Curiously, chapter 6 revealed that average levels of neuroticism correlated positively with ability to self-reassure in healthy controls, suggesting that neuroticism has the potential to be adaptive as well as maladaptive. Findings from a systematic review and fMRI study of defensive behaviour healthy controls and an experimental study in GAD both indicated the potential of a neural network for neuroticism in mood and anxiety disorders, with a focus on the insular cortex. The argument that neuroticism forms the ‘core’ of the VDT was also investigated, with partial support for this hypothesis; it appears likely from the results of chapter 7 that more than one ‘core’ trait is relevant to expression of VDT traits.

The impact of raised neuroticism was highlighted in moderation of disorder-specific characteristics, relating to greater self-criticism in GAD and co-morbidity, supportive of previous work (Claridge & Davis, 2001). The personality traits of conscientiousness and agreeableness were identified as additional factors in the negative relationship between neuroticism and self-criticism, and as such are discussed as straight-forward additions to screening routines using neuroticism to identify those at risk of depression and anxiety disorders. Agreeableness was also identified as a trait of interest in the expression of VDT constructs. Further, aspects of negative self-reflection such as self-criticism were explored as possible disorder-specific dimensions. Self-hatred was shown to be higher in individuals with co-morbid history of MDD and GAD, whilst more negative comparison of self- to- peers as measured by the FIQT was associated with both single-diagnosis MDD and co-morbid history of both MDD and GAD. As such, negative self-reflection may provide additional specificity to measures of neuroticism in identifying vulnerable individuals.

Finally, this thesis piloted two tools, one designed to measure self-reflection via perceptions of performance, and the other to explore active defensive behaviour as an alternative to self-report approaches. The FIQT measure of self-reflection was successfully piloted, though future work is recommended to explore the relevance of ego-involvement in this task. The JORT measure of defensive behaviour was explored in a sample of individuals with GAD in an fMRI paradigm for the first time, with the results indicating refinement of the tool is required.

The findings outlined in this thesis support neuroticism as a transdiagnostic factor in GAD, MDD and co-morbid history of both. The ability to distinguish between these disorders using lower-tier individual differences was also explored and was discussed in relation to treatment approaches. Following the success in chapter 3 of using neuroticism to identify individuals with GAD using self-reported neuroticism, the potential application of these findings to the refinement of this current tool to use a two-tiered approach similar to previous recommendations (Barlow et al., 2014; Caspi & Moffitt, 2018) is outlined. Development of a highly precise method of identifying treatment-naïve individuals using a non-invasive online self-report tool would be a boon to clinical research.

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Appendix

Example text from email sent to participants completing online self-report personality measure.

Your Online Personality Questionnaire Results-

Your score on Openness to Experience places you in the middle range, indicating you have a combined style of thinking: sometimes you like to think in plain and simple terms, when the circumstances dictate, while at other times you like to think in more complex, abstract ways. You like a combination of these styles of thinking and combine them in ways to best suit what you are doing. Sometimes you are down-to-earth, practical, and a no-nonsense type of person. At other times, you prefer more novel and stimulating things. This combination of being a "doer" and "thinker" puts you in a potential strong position in your occupational, social and personal life. It is a very flexible way of perceiving, thinking and behaving towards the world, and means that you can apply yourself to different tasks with ease and flexibility.

In terms of enhancing your potential, you might want to consider experimenting separately with exclusively novel/stimulating tasks and routine/practical tasks. Such experimentation would strengthen your cognitive skills in these two different areas, and this would serve to improve your overall performance when both sets of skills are required, as well as allowing you to deal with situations that require a high level of proficiency in one of other of these areas.

Your score on Conscientiousness places you in the middle range. This means you are reasonably reliable, organized, and self-controlled. You neither like to live for the moment and do what feels good now nor become too stuck in mundane routine and attention to detail. Your occupational, social and personal lives tend to be well-organised, and where things go wrong you have the capability to go about remedying matters in a sensible fashion.

In occupational contexts, you have the ability to switch between attention to detail, when this is necessary, and seeing the bigger picture, when this is necessary: this is a great asset. One possible downside is in those areas where either extreme attention to detail or the bigger picture is needed. Here you might want to experiment with acquiring the ability to attend to detail only and then to ignore detail and focus on the bigger picture. This acquired ability would place you at great advantage when situations arise that demand one of these two extreme forms of behaviour.

Your score on Extraversion places you in the middle range, indicating you are neither a subdued loner nor a jovial chatterbox. You enjoy time with others, but also time alone. Your behaviour can depend on the situation, and you are neither always introverted nor always extraverted. You have a good balance of Extraversion that allows you to respond appropriately to different demands made upon you. How

you typically behave will be influenced by your scores on the other four dimensions of personality, especially Agreeableness, Openness to Experience, and Neuroticism.

When you are in a slightly introverted mood, you prefer being reserved and quiet and you may enjoy some solitude and solitary activities. You are neither a raving party-goer or wall-flower, all of the time, but you can switch between these behaviours as you see fit. You probably have a few good friends, as well as wide circle of acquaintances. In occupational settings you have the ability to modify your behaviour according to what is required, and people will see you as sociable, but not overly so. If you are high on Agreeableness, people will see you as a likable person, who gets on with many people.

The challenges that you face is being able to use the information provided from your other four dimensions to decide what's most appropriate in the specific occupational, social or personal context you find yourself in. Your Extraversion score does not incline you towards great introversion or Extraversion, and this gives you considerable potential flexibility in dealing with social situations in the most appropriate manner.

Your level of Agreeableness places you in the middle range, indicating some concern with others' needs, but, generally, unwillingness to sacrifice yourself for others. You can be tough, critical, and uncompromising when the situation demands, but also tender-minded, accepting and compromising at other times. How you typically behave will be influenced by your scores on the other four dimensions of personality, especially Openness to Experience, and Neuroticism.

Your flexibility, and ability to modify your behaviour depending on what the situation demands, meaning that other people will see you as a particular asset and not something who is stuck in one mode of behaving irrespective of what the situation demands. Although extreme ways of thinking, feeling and behaving are usually inappropriate, you might want to play around with developing some very tough-minded ways of thinking and behaving, as well very tender-minded ways, so that if situations arise that call for such extreme responses then you are prepared to respond. Developing the capacity to switch between these states may be especially beneficial in different areas of your occupational, social and personal life.

Your score on Neuroticism is low indicating that you are exceptionally calm, composed and unflappable. You do not react with intense emotions, even to situations that most people would describe as stressful. People consider you to be a calm person. You are able to remain focused, and not to lose control even when those around you are starting to panic. This is a great attribute to possess in most situations because it means that in time of adversity you are able you use your thinking skills to solve problems without them becoming overwhelmed by negative emotion. You also see changes in life with a more positive disposition, and importantly you do not see change as a threat to you, rather as an

opportunity for improvement. Other people trust you in a crisis, and when combined with high Openness to Experience, you have the potential to be a successful leader.

On the downside of being emotionally stable are: not reacting appropriately when the situation calls for the generation of negative emotions - these emotions exist to motivate us into taking appropriate action to remove the unpleasant source that is leading to the emotion. Also, other people may see you are somewhat uncaring or even a "cold fish", especially if you are low on Extraversion and/or Agreeableness. Being able to generate some negative emotions appropriately, but not to excess, is no bad thing; if nothing else it conveys to others that you not only share their concerns, but you have the ability to 'feel' their experiences. Developing this empathy with others is often essential to success in occupational, social and personal contexts.

I hope you enjoyed taking this personality questionnaire and found the results interesting and of some value to you. They are only a starting point to further developing your psychological skills and achieving your full potential. Remember though, whatever your scores, you are a unique person who does not fit exactly into any convenient categories. A questionnaire such as the one you have just completed can indicate only general areas of personality. Whilst these are undoubtedly important in your life, it is equally important that you feel comfortable with your personality and use the information contained in your personality profile to devise ways of using your existing potential to enhance those areas of your life that you particularly value and cherish.